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THE DISTRIBUTION AND QUANTITATIVE ACTION OF THE VAGI AS DETERMINED BY THE ELECTRICAL CHANGES ARISING IN THE HEART UPON VAGUS STIMULATION

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In a survey of the literature upon the vagus nerves, one can not but be struck by the fact that so many workers in this field have paid so little attention to a clear discrimination between the right and left vagi. General conclusions have been drawn, with regard to vagus activity, which are applicable only to the left vagus, and in the earlier publications no attempt even was made to differentiate between vagus and accelerator nerves, so that functions peculiar to different nerves have been assigned to both vagi.

The idea that the vagus nerves may or may not exert contralateral effects was not put to the test of experiment till 1911, when Garrey (1) carefully considered the matter, using the whole and partially split heart of the turtle and recording his results graphically. His conclusions, which are very definite, are as follows. He asserts first, that the origin of the beat is to be found in the right caval veins, the inherent rhythmicity of which he showed to be greater than that of the sinus and auricles and then he shows that, in the whole heart, the right vagus affects chronotropically, through its action on the right veins, every part of the organ, while the left vagus may affect the whole, including the right veins, but that usually it affects the left veins, the sinus and the auricles, producing quiescence by decreasing the excitability, conductivity and contractility of the auricles, leaving the rhythm of the right veins unaffected. In the "ascidian preparation" of the turtle's heart, in which the beat travelled from right to left, very clear conclusions were arrived at, namely, that the right vagus stopped the whole

preparation, while the left inhibited the left auricle and right auricle, the right basal veins still continuing to beat at their original rhythm. This, according to Garrey, is due to the fact that the left vagus does not affect the pace-maker, but acts upon structure similar to that upon which normal cardiac impulses act. The essential point determined is that the vagi act chronotropically on their respective sides, upon those parts which initiate the rhythm. This is the basis of the homolateral view of the action of the vagi, which has been so strongly brought forward by Garrey who, however, showed that such effects were not so clearly marked with regard to the auricles, and he states "that the experiments bring out clearly that in auricles as well as in veins and sinus the vagus effects may cross to the contralateral side."

Robinson and Draper (2), from an investigation of the action of the vagus nerves upon the human heart, corroborate previous findings on the mammalian heart, namely, that the predominant action of the right vagus is a control of rate, through its inhibitory action upon the normal pace-maker of the heart, and that of the left nerve is primarily a control of conduction from auricle to ventricle, through a direct inhibitory effect upon the conducting system and that in gauging the difference upon conductivity of the right and left vagi, the factor of heart rate must be taken into account. Again, with regard to auriculo-ventricular dissociations, it was shown that these are not caused by diminution in the conductivity, but are essentially due to the inherent high rate of rhythmicity of the ventricles, dissociation occurring as soon as vagus stimulation reduced the auricular rate below that at which the ventricles will contract by their own inherent rhythmicity. This viewpoint is supported by experiments of Rothberger and Winterberg (3) who demonstrated true nodal rhythm by stimulation of the right vagus and left accelerator nerves.

Cohn (4) in 1912 stated that negatively chronotropic effects may be obtained upon stimulation of the left vagus and he made this significant statement "that it is doubtful whether the distribution that has been described is as refined as is necessary to explain the results" he obtained.

With regard to the importance of heart rate in gauging dromotropic effects of the vagi, attention is drawn to a paper by Robinson (5) in 1916, in which he shows that there is no constant difference between the right and left vagus nerves in their action upon conductivity between the auricles and ventricles during auricular fibrillation.

The first report upon the electrical changes in the heart due to vagus stimulation was made by Gaskell (6). The type of experiment which

he describes depends upon the peculiar arrangement of the vagus nerve in the tortoise heart, where a branch of the vagus runs with the coronary vein from the sinus to the base of the ventricle. This "coronary" vagus being free, the sinus and left auricle could therefore be cut off without damage to the nerve supply of the right auricle, thus allowing of a quiescent preparation. A demarcation current having been produced by "thermic section" and the right vagus stimulated, a deflection was obtained in the same direction as that of the injury current, indicating increased positivity of the uninjured part. These experiments were carried out by means of a d'Arsonval galvanometer.

Gotch (7) in 1887, using a capillary electrometer, could not obtain this vagus effect, the position of the meniscus, upon vagus stimulation, remaining at the position obtaining during diastole. It was suggested by Burdon Sanderson (8), during a discussion of this subject, that the capillary electrometer was probably not sufficiently sensitive to detect such slight changes of potential as had been detected by Gaskell by means of a much more sensitive instrument.

Einthoven (9) in 1908 criticised Gaskell's results and doubted their accuracy because, by means of the string galvanometer he was unable to detect any changes of potential whatsoever. That Gaskell was correct was clearly demonstrated in 1911 by Meek and Eyster (10), who with an Edelmann galvanometer, using the tortoise heart prepared according to Gaskell's method, obtained uniformly positive results. Theirs was an exceptionally clear corroboration of the Gaskell phenomenon, as evidenced by a rapid deflection of the string and its slow return to the original position. If the heart were beating, this prolonged slow fall of the string to its original level would be cut short by the first beat following upon inhibition and the return of the base line to the zero position would be rapid. That this happens in the beating heart was shown by Samojloff (11), who used the same type of instrument. The hearts of decapitated frogs were utilized, an injury current was produced by the application of a drop of 1 per cent KCl to the apex of the heart, and leads taken, one from the apex the other from an uninjured part of the heart. A monophasic variation was obtained with each beat, and upon stimulation of the right vagus the zero line was deflected in the direction of the injury current; the deflection was slow and emphasis was laid upon the fact that the return of the string did not begin until a contraction supervened.

PART I

Electrical changes associated with the action of the vagi

The fundamental principle involved in determining these changes depends upon the following acceptation.

With a demarcation current or injury current. In normal muscle excitation is evidenced by an increased negativity of the part involved and electrodes can be so arranged that such negativity gives rise to an upstroke of the string of the galvanometer. When in the heart an injury current is produced, the injured surface becomes electrically negative to the uninjured part and the difference of potential thereby occasioned gives rise to a deflection of the string in a direction opposite to that which denotes excitation in normal muscle. A wave of excitation passing over such a field would produce at the positive or uninjured part a decrease of its positivity with respect to the injured spot and therefore cause a rise in the direction of, but smaller than, that due to a normal contraction. If the vagus nerve be stimulated, its effect is to reduce the condition of negativity and therefore relatively increase the positivity, the result being a deflection of the string in the same direction as that of the injury current.

In the normal or uninjured condition. To obtain monophasic variations from the action of the heart muscle, one electrode must be placed on the heart, the other on a part of the body wall sufficiently removed from the heart to allow of the activity of all parts of the heart muscle being marked by an upward deflection. If now the electrical changes of the heart, due to its activity, are not totally inhibited, these will show themselves as upstrokes of reduced amplitude, arising from a zero line at a lowered level.

It may be assumed that whatever occasions the beat produces a sudden catabolic change, a change dependent upon a previous building up of excitability or, to use Gaskell's term, a process of assimilation. There is no reason to suggest that such a process of assimilation should be of such a sudden nature as that of the catabolic discharge or dissimilation; the deflection caused by the one may be wholly different from that caused by the other, the factor chiefly concerned being that of velocity. It is supposed that these anabolic changes are inaugurated by vagus action and therefore that electrical stimulation of the vagus increasing these, it should be possible, using a galvanometer of sufficient sensitivity, to detect the changes in potential arising therefrom.

During inhibition the heart suffers an alteration of its excitability and its activity is depressed. It may therefore be feasible to accept the interpretation of Samojloff's curves, that contractions may be resumed at an increased level of anabolism, provided the process has reached completion and stopped, as otherwise it is difficult to conceive of contractions supervening during a process which is essentially of the nature of an inhibition. If the building up of excitability or the inhibitory process has not reached its maximal development, then, to explain the breaking through of heart beats, one must assume that the vagi and the contractions act upon different mechanisms in the cardiac muscle. Gaskell (12), McWilliam (13), (14), and Roy and Adami (15) state that excitability is diminished during inhibition but all that they can prove is, that the heart in inhibition was inexcitable, and that, during a period when it was establishing a necessary condition such that the subsequent stimulus should produce a contraction, that is, a condition of excitability. Therefore their diminished excitability is associated with what may be regarded as a refractory period of inhibition. Just as there is a refractory period in catabolism so one postulates a similar condition in anabolism. This would support the idea suggested that the upstroke is indicative of the true inhibitory period, i.e., the time till maximal deflection is reached, after which the excitability of the tissue is such that stimuli may be effective, which stimuli, however, may be delayed over a longer or shorter period, according to the degree of diminution of conductivity, which is a manifest effect of both vagi.

The results of the experimental work to which reference has just been made, demonstrate clearly the occurrence of electrical changes in the heart during vagus stimulation. These changes then may be employed to determine the distribution of the vagi in the heart, to demonstrate the action of these nerves upon its various parts and to decide if possible by what means vagal impulses are propagated. To do this a preparation of the whole and also of the partially split heart has been used.

Experiments carried out with the d'Arsonval galvanometer

From previous work done, using the string galvanometer for determining the electrical changes occurring in the heart upon vagus stimulation, it was found that, in the normally beating heart, the string galvanometer is too sensitive an instrument to withstand the action

current of the heart, when the string is slackened to that extent which is necessary to give definite evidence of the positive variations. With sensitivities such that 1 m.v. gives deflections from 5 to 10 cm., the results are in many cases not convincing. It was therefore determined, seeing that it was impossible to carry out these experiments upon a quiescent heart, to utilize a very sensitive d'Arsonval galvanometer and, by means of a rheotome, to place it in circuit with the heart only, during the very brief period of its quiescence between beats.

Methods

The rheotome. This consisted of a brass segmented wheel having one continuous central contact and two, one on either side of the former, in which there was placed a different length of fiber, so that by adjustment of these, any length of non-conducting material could be readily obtained. Thus by using three contacts, the two external being connected, a definite period of time could be obtained during which the galvanometer could be thrown into the circuit. This period was chosen so that the ventricular, auricular and sinus effects could be eliminated. The circumference of the rheotome was 500 mm., the gap was, after experiment, cut down to 45 mm.

The quiescent period of the heart. To throw the galvanometer into circuit at this point of the cardiac cycle, a simple make and break device was arranged whereby the relaxation of the ventricle completed the circuit between six storage cells and a solenoid, which lifted the catch checking the rheotome wheel. This allowed the wheel to rotate, the retaining pawl being so placed that immediately it was lifted upon ventricular relaxation, the galvanometer was put in circuit with the heart. The rotation of the segmented wheel was so arranged by a switch upon the power table, that one revolution was just completed within the period of the cardiac cycle. The pawl, which was dropped upon contraction breaking the circuit, stopped the wheel for a very brief moment, depending upon slight variations in the heart rate.

It was found that in the majority of cases it was necessary, in order to obtain a quiescent period, to cool the heart, because, in a heart beating at the rate of thirty per minute, the sinus was in action sometimes during a ventricular contraction, or following so closely upon ventricular contraction that the rheotome method was rendered of no avail. The sinus was cooled by means of a blind perfusion cannula, through which was maintained a continuous flow of ice-cooled water

of a temperature of about 10°C. The cooled point was maintained upon a definite spot on the sinus, a spot previously determined as being the seat of highest rhythmicity.

The sensitivity and calibration of the galvanometer. The d'Arsonval galvanometer used in these experiments was the type "R" of the Leeds & Northrup Company, which had a sensitivity of 5×10^{-10} amperes per mm. and a voltage sensitivity of 0.5 mm. per microvolt, with a period of 5 seconds. Calibration of the instrument, with the rheotome running, gave readings for 0.1 m.v. of 7.3 cm. in 5 minutes and a return to 0.5 cm. from zero in 6.0 minutes. Therefore a deflection of 7.3 cm. = 0.1 m.v. and is equal, without the rheotome to a deflection of 22 cm. From this it is seen that to obtain full values with the rheotome method, it would be necessary for the vagus effect to last 5 minutes. From the rate of rise of the curves and from their magnitude it will be seen that the "vagus" effect is a very marked one, is maintained and is dissipated quickly by subsquent beats.

A difficulty which arises with the rheotome method is, after vagus stimulation, to cut out the prolonged beats of the auricle which usually encroach upon the quiescent period of the heart, even abolishing it, and so cause a sudden return of the beam of light, which may reach its original position or pass beyond it in two or three steps. One can, however, by operating the rheotome with a key, cut out the auricular beats occurring immediately after inhibition, the solenoid circuit being broken upon the first sign of movement in the basal veins.

Compensation of the injury current. With a very slowly moving coil galvanometer, with the time of stimulus very short, namely 0.18 second when the rheotome was making thirty revolutions to the minute, the response to small currents may be so small as scarcely to be noticed. In compensating, therefore, one must accurately gauge the period of the heart cycle in which no electrical effects from auricular beat are allowed to encroach upon the period of quiescence. The sinus effect is so small that deflections caused thereby can be ignored, but small inclusions of auricular effects would simulate over-compensation. This, as well as the opposite effect of under-compensation, must be guarded against, because the latter, if not accurately gauged, will give deflections in excess of those due to vagus stimulation, since a deflection denoting an increased positivity is an extension of that of the injury current.

Type of reading obtained. It is essential, if maximal deflections are to be obtained, to stimulate the vagus, maintaining the quiescence of

the heart, till there is no further increase in the amplitude of the deflection. This may necessitate a vagus stimulation up to from 60 to 80 seconds, although maximal deflections are usually obtained well within this period. The type of reading resulting from this method is shown on the tracings, these records having been made by a device of Gesell (16), in which the beam of light can be followed and the curve recorded upon a moving drum. The record is in the form of a series of steps which are of varying sizes and are in the form of curves as shown in several tracings. It was not practical to follow accurately these fine swinging movements of the beam of light. The first few initial steps are steep; they then rapidly become less and less in size till, at the plateau of the curve, the small pendular movements synchronous with each revolution of the rheotome only are in evidence. The plateau may be maintained for a longer or shorter period and is, unless the rheotome is controlled by hand, suddenly terminated by the first auricular contraction.

Type of reading without the rheotome. In the partially split heart, where the wave of contraction sweeps from right to left, it is of course possible to prevent auricular or ventricular effects of the side under observation, from affecting the galvanometer, but it has been found that after 2 or 3 hours, when the activity of the heart has become considerably lessened, the ventricle has little effect upon the galvanometer, the sinus none at all and the auricular contractions show as small deflections, with a total amplitude of from 1 to 1.5 cm. With such a weakly contracting heart, beating at about sixteen per minute, the mean of these deflections can be taken, because the beats are usually so weak that any cumulative effect takes a considerable time to show any alteration in the mean level of the beam of light. Thus the changes occurring upon vagus stimulation are quite easily discernible.

The whole heart

Table 1 shows that the right vagus is always markedly active upon the right auricle and in many cases very slightly less so upon the left auricle. The point of note with regard to the left auricle is that, in about a fourth of the cases, the right vagus is more effective than the left, and generally the left vagus is always less marked in its action upon the left auricle than is the right vagus upon the right auricle, while upon the right auricle the left vagus is, with three exceptions, decidedly weaker in action than either the right or the left vagus acting upon

its respective side. The tracings reproduced here as figures 1 to 5, with attached explanatory notes, illustrate the basis upon which these conclusions rest. All were obtained through the d'Arsonval galvanometer.

TABLE 1

Results with the d'Arsonval galvanometer, with an injury current

	RIGHT VAGUS		LEFT VAGUS		REMARKS
	Right auricle	Left auricle	Left auricle	Right auricle	
	cm.	*cm.*	*cm.*	*cm.*	
1	4.5	3.5	5.5	3.0	Heart cooled. Rheotome rate 24 revolutions per minute
2	7.5	5.0	4.0	3.5	Heart quiet with muscarine; no rheotome
3	4.5	4.0			
4		10.5	5.5		Heart rate 16 per minute
		11.5	5.0		Temperature 10°C.
5		9.0	8.0		Without rheotome; heart quiescent; right auricle cut away
		8.5	9.5		
		8.5	11 0		
		9.0	9.5		
6	2.5			1.0	Gaskell's preparation; coronary vagus intact
	1.5			0.5	
7		0.8	1.0		Sinus cut off from right auricle; coronary vagus intact; left auricle quiet for short periods
		1.0	1.5		
8		7.8	8.8		Heart rate 15 per minute, temperature 10°C.
9		8.5	6.0		Heart rate 20 per minute; heart cooled
		6.5	5.5		
10	6.5	6.5	4.5	3.5	Heart rate 20 per minute; heart cooled
11	6.5	5.0	4.0	4.5	Heart rate 20 per minute; heart cooled
12	6.2	5.5	4.5	5.0	Heart rate 20 per minute; heart cooled
13	3.5	2.5	3.3	2.8	Heart rate 20 per minute; heart cooled
14	5.5	3.0	2.5	2.0	Heart rate 20 per minute; heart cooled
15	2.0		2.0		Heart completely split
16	3.5		2.0		Heart completely split
	2.0		1.0		
17	4.8		3.3		Heart completely split
	4.0		2.5		
18	5.5	5.5	4.2	4.0	Heart cooled
19	2.2	1.8	1.9	1.6	Heart cooled
20	2.5			2.0	Heart cooled
21	3.3	2.0	3.2	2.0	Heart cooled
22	2.1	1.0	2.2	0.6	Heart cooled
23	1.8	1.2	1.4	0.9	Heart cooled
24	1.6			0.8	Heart cooled
25	2.9	2.0	1.9	1.2	Without the rheotome
26	2.6	2.3	2.1	2.0	Without the rheotome

Fig. 1. Whole heart; right auricle, injury current; right vagus stimulation. This is a typical result of the rise and fall during the quiescent period of the heart. Here the only part of the curve not due to vagus activity is the first downstroke occasioned by the commencing auricular beat. The vagus was stimulated for 36 seconds, the deflection obtained being 3.2 cm.

Fig. 2. Whole heart; right auricle, injury current; left vagus stimulation. This record shows the steady rise step by step indicating increased positivity of the left auricle. The inhibition of the left side was maintained for a period of 58 seconds, while stimulation of the vagus lasted for 60 seconds, producing a maximal deflection of 2.6 cm.

Fig. 3. Whole heart; left auricle, injury current; left vagus stimulation. This is a very good example of the steady step-like movement of the beam of light. The vagus was here stimulated for 36 seconds, the duration of the rise was 24 seconds and the maximal deflection was 2.7 cm.

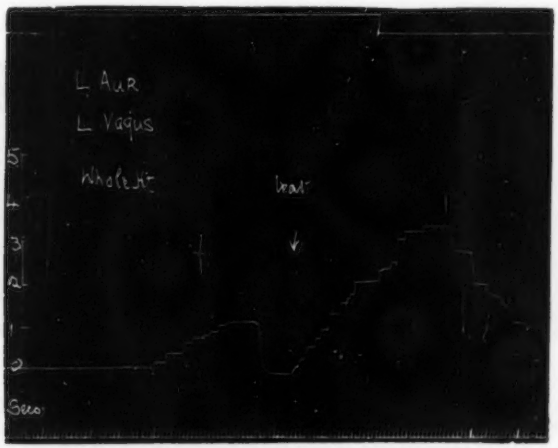

Fig. 4. Whole heart; left auricle, injury current; left vagus stimulation. This tracing is of interest in showing the effect of one beat of the heart breaking through in a short inhibition, which is then followed by a steeper and longer rise giving a total deflection of 3.2 cm. Stimulation of the vagus was continued for 64 seconds and there was no apparent sign of shifting of the electrodes or temporary stoppage of stimulation to account for the single beat.

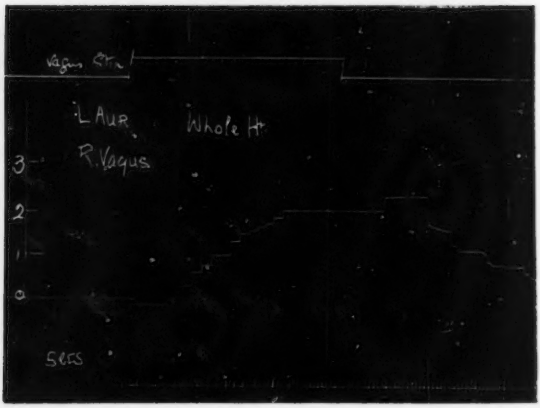

Fig. 5. Whole heart; left auricle, injury current; right vagus stimulation. The total deflection of 2.0 cm. was obtained in 30 seconds. The rise and fall are both typical, the fall below the original base line being due, probably, to a diminution of the demarcation current.

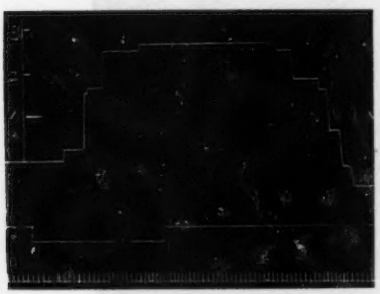

Fig. 6

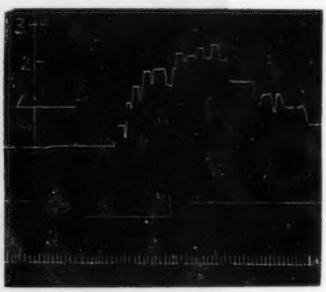

Fig. 7

Fig. 6. Partially split heart; rheotome; right auricle, injury current; right vagus stimulation. In this case the injury current was not compensated. The vagus acted for 12 seconds and gave a maximal deflection of 2.6 cm.

Fig. 7. Partially split heart; rheotome; right auricle, injury current; right vagus stimulation. Here the pendular movements were followed as accurately as possible. This record shows exactly the type of movement which is performed by the beam of light upon the scale, as the galvanometer responds to every brief impulse which it receives with each revolution of the rheotome. The inhibition was maintained for 26 seconds and the rise was completed in 15 seconds, the total deflection being 2.3 cm.

The partially split heart

With the rheotome. The type of results obtained from the partially split heart when the d'Arsonval galvanometer is put into circuit by means of the rheotome is seen in figures 6 and 7 and table 2, and described in the legends to the figures.

Types of deflections obtained without the rheotome. Using the rheotome, the results have, in the case of the action of the vagi on the contralateral sides of the heart, been invariably negative. In fact there is to be seen a slow movement of the beam of light in the direction opposite to that

TABLE 2

Results with the d'Arsonval galvanometer, with an injury current; split heart

	RIGHT VAGUS		LEFT VAGUS		REMARKS
	Right auricle	Left auricle	Left auricle	Right auricle	
	cm.	*cm.*	*cm.*	*cm.*	
1		3.0 2.0	1.5		These readings correspond with those obtained previous to sagittal section. Therefore (?) faulty section
2	4.5	0.0	6.5	0.0	
3	4.0	0.0	5.0	0.0	
4		0.5	3.5	0.0	
5		1.0	4.0	0.0	
6		0.0	5.0	0.0	
7	3.5	0.0	2.0	0.0	
8	3.0	0.0	2.5	0.0	
9	5.0	0.5	3.5	0.0	
10	2.0	0.0	2.0	0.0	
11	2.8	0.0	4.4	?	
12	3.3	0.0	3.2	0.0	

indicating a positive variation, due either to a diminution of the injury current or to the effects of weak contractions from parts of the heart, other than the auricle under obsevation. The best and most decisive results in the partially split heart have been obtained, without the rheotome, 2 to 4 hours after opening the pericardium and about $\frac{1}{2}$ hour after making the sagittal section, because by this time the beats, running from right to left, have lost much of their vigor and rapidity.

The current of injury is not compensated and from the tracings (figs. 8 to 13) it will be seen, that the movements, due to contractions, are very small indeed.

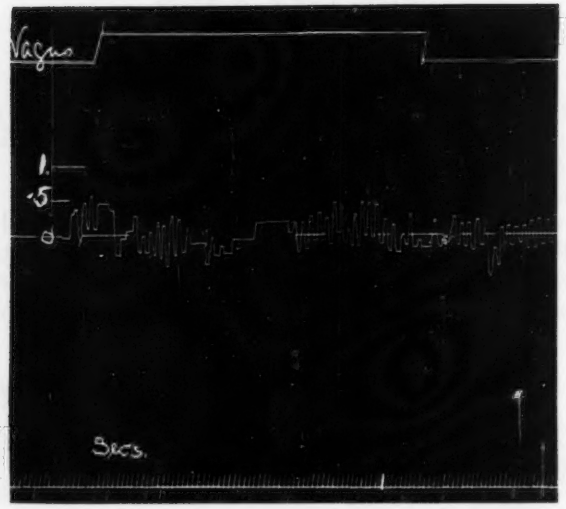

Fig. 8. Partially split heart; without rheotome; right auricle, injury current; left vagus stimulation. The movements of the beam of light were successfully followed in this case and it will be noted that there is neither inhibition of the right auricular beat nor alteration of the base line due to a stimulation of the left vagus lasting 52 seconds.

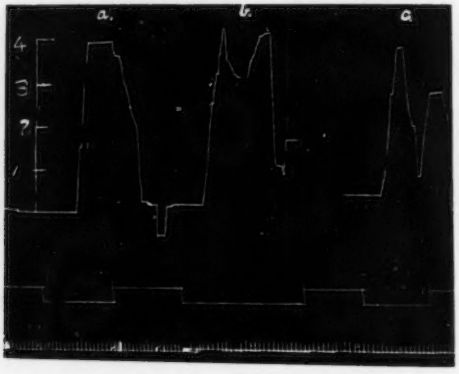

Fig. 9. *a*, *b*, *c*. Partially split heart; without rheotome; right auricle, injury current; right vagus stimulation. These three are typical of results obtained without the use of the rheotome. The height and rapidity of the deflections are comparable to those obtained by Gaskell, and show a definite electro-positive change. The deflections have a maximum of 3.8, 4.0 and 3.3 cm. with a time of 3.0, 4.0 and 3.5 seconds, respectively. The tendency, even in a weakly beating heart, for the "vagus" effect to be repeated, is seen in these tracings.

Fig. 10. Partially split heart; without rheotome; left auricle, injury current; left vagus stimulation. The action of the left vagus upon its own side, as graphically shown here, is similar to that obtaining in the whole heart. The response is rapid and the time taken to attain a maximal deflection of 3.8 cm. is 4.0 seconds.

Fig. 11. Partially split heart; without rheotome; left auricle, injury current; left vagus stimulation. This shows activity of the left vagus upon the left auricle three and one-half hours from the commencement of the experiment. The pendular movements are due to the right auricular beats.

Fig. 12. Partially split heart; without rheotome; left auricle, injury current; right vagus stimulation. The survival of the left auricular contractions in the partially split heart, upon right vagus stimulation, is clearly seen here. The more rapid beats due to the right auricular rhythm are seen at the beginning of the tracing and their almost immediate inhibition upon right vagus stimulation is clearly shown, the slower left auricular rhythm remaining. That in this "ascidian" preparation the right vagus has no effect upon the uniform position of the base line, which is the mean of the auricular deflections, is demonstrated in this experiment, where the right vagus stimulation lasted for 58 seconds.

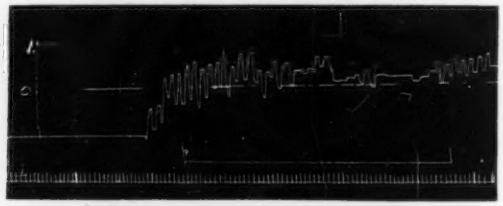

Fig. 13. Partially split heart; without rheotome; left auricle, injury current; right vagus stimulation. The fact that the right vagus has no action on the left auricle in the partially split heart is again shown here. After the deflection of the injury current was obtained, the movements of the beam of light were followed and the right vagus stimulated for 60 seconds. No alterations in the base line took place. The right auricular contractions were inhibited and the latter half of the tracing shows only the left auricular deflections, which with their slower rhythm come into evidence toward the end of the tracing. This occurs after a period of stand-still of very brief duration, during which time the inherent rhythmicity of the left auricle becomes established.

PART II

The quantitative effects of the vagi

The foregoing results with their demonstration of crossed vagal effects suggested a quantitative study of these.

To determine what quantitative vagus changes may occur on both sides of the heart the graphic method was used and the curves plotted on coördinate paper. As the rheotome revolved at a rate of either twenty or thirty revolutions per minute, and as both vagi, in most of the experiments, completely stopped the heart, the repeated contacts were made at regular intervals, thereby giving one a means of comparing the rate of deflection of the beam of light step by step, each step denoting a definite period of time during wh'ch the galvanometer was in circuit with the preparation. To arrive at some idea as to the intensity of the vagus action, it is necessary to compare the deflections, using as a standard a definite period of time during which the nerves are stimulated, and to do this the most convenient method is to take a number of steps or a number of revolutions of the rheotome, but not more than that required by the lowest curve to attain its maximal deflection. Without the rheotome, to take a definite height as a standard and compare the time required to reach it, would be admissible, but with the rheotome a standard height precludes any comparative conclusions, because it manifestly gives the slower effect the advantage of a greater number of contact periods.

The curves are plotted for the position of the beam of light either every 5 seconds or for every revolution of the rheotome; the abscissae denote time in seconds and the ordinates deflections in centimeters. The stimulation of the vagus, marked by a signal, was usually continued till the maximal effects were obtained, the time was recorded by a Jacquet chronograph and the records were made by Gesell's method already referred to. The results obtained can best be presented as descriptions of the curves.

Figure 14. Here the right vagus was stimulated for 36 seconds, and the electrical change commenced 13 seconds after stimulation began, and in 38 seconds the maximal deflection had been obtained. The curve both in its gradient and height is typical of the right vagus effect. In 15 seconds the beam of light had risen 2.9 cm., after which the change became more and more gradual, till 10 seconds later, the maximal deflection of 3.3 cm. was attained, where it was steady for 5 seconds and then fell at first quickly, later more and more slowly

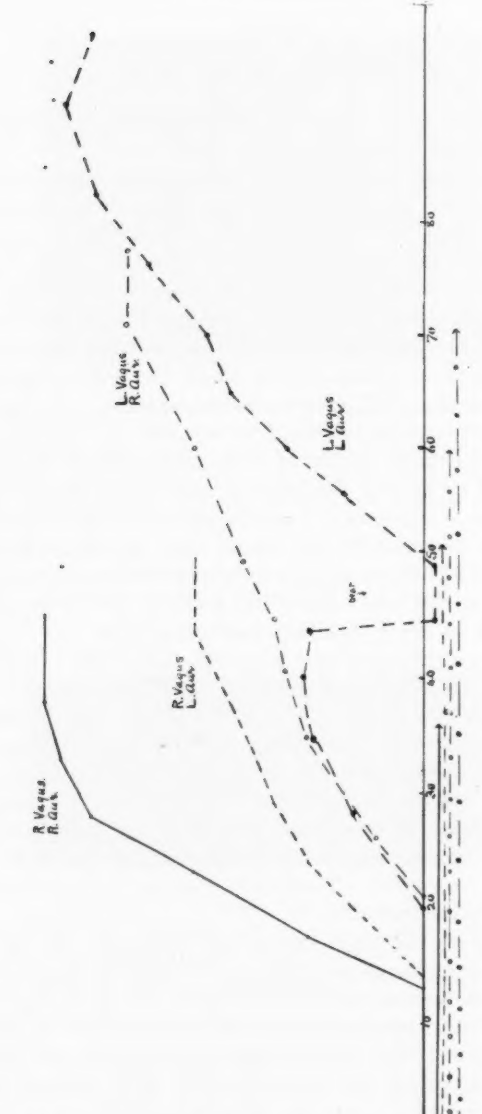
R Vagus
R. Aur
R. Vagus
L. Aur
L. Vagus
R. Aur
L. Vagus
L. Aur
Deflection = Cms
Time Secs.
Duration of Stimulation

Fig. 14

as the base line was approached. The right vagus effect upon the left auricle shows a change commencing as soon almost as that of the right vagus upon the right auricle. The gradient of the electrical change is less marked though quite as definite as that of the homolateral effect. The total stimulation lasted 52 seconds and the maximal height of 2 cm. was reached in 30 seconds. The left vagus in this experiment had a longer latent period but, like the right vagus, the period was practically the same for both sides, 20 and 21 seconds respectively. This is the case previously mentioned, in which a beat was interpolated 24 seconds after inhibition had been produced. The action current of the heart caused an immediate return of the beam of light to just below zero, inhibition was again produced and in 5 seconds it is evident and much more markedly so than in the previous rise. Comparing the left vagus effect upon the right and left auricles, it is seen from this figure that the second rise due to the left vagus is steeper than that of the left vagus effect upon the right auricle. This is the usual result obtained, though not without exception. The maximal rise and the time taken for each vagus on both sides of the heart are as follows:

	cm.
Right vagus acting upon right auricle for 18 seconds	3.3
Right vagus acting upon left auricle for 30 seconds	2.0
Left vagus acting upon left auricle for 40 seconds	3.2
Left vagus acting upon right auricle for 49 seconds	2.0

Figure 15. For comparative purposes the deflections occurring upon each of five consecutive revolutions of the rheotome are plotted. The marked ascendancy of the right vagus upon the right side of the heart is well shown; also from the graph of the second rise of the left vagus upon the left side, which has been traced in for comparison in the position of the original rise, it can be seen that the very definite effect upon its own side is greater than the right vagus effect upon the left both in maximal deflection and in rapidity of its rise. The left vagus action upon the right side is the least marked of all and this record, with the second curve of the electro-positive change of the left vagus transcribed, sums up very clearly the various effects occasioned by both vagi, each acting upon both sides of the heart.

Noting the deflections after five revolutions of the rheotome, the heart being inhibited by both vagi and the time interval between the stimuli being the same for all, namely, 2 seconds, the galvanometer being in circuit with the heart for a period of 0.18 second, we have the following results·

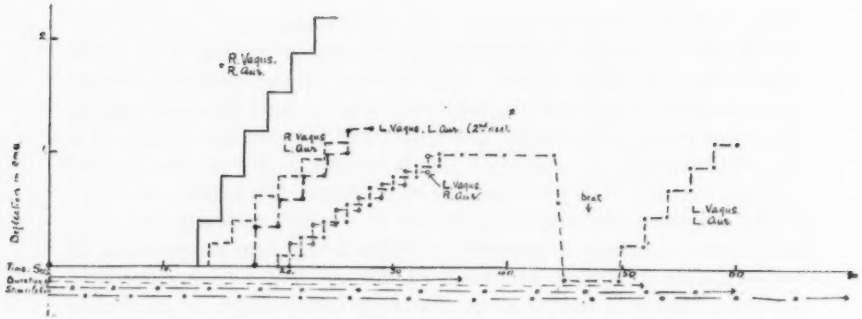

Fig. 15

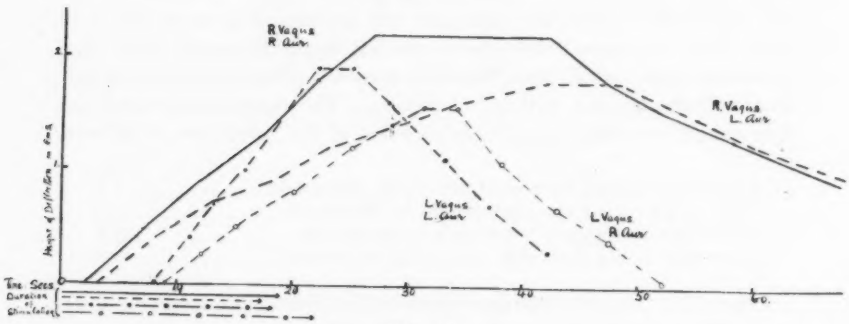

Fig. 16

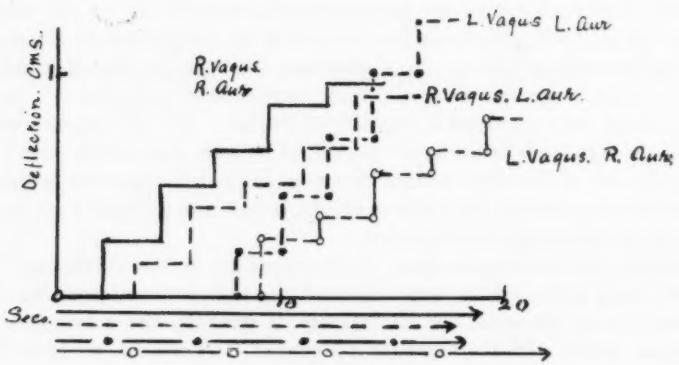

Fig. 17

	cm.
Right vagus acting upon right auricle	1.9
Right vagus acting upon left auricle	0.9
Left vagus acting upon left auricle	1.1
Left vagus acting upon right auricle	0.7

Figure 16. As in the preceding record, the greater latent period of the left vagus as compared with that of the right is shown and here the left vagus action upon its own side is very definite, especially with regard to the velocity of the change, in which in this case it exceeds that of the right vagus upon the right side. The slower contralateral effects, though of scarcely less magnitude are noteworthy, when one recalls what has been suggested with reference to the anatomical distribution of the vagi. The maximal deflections and the time taken for their completion are as follows:

	cm.
Right vagus acting upon right auricle for 25 seconds	2.2
Right vagus acting upon left auricle for 39 seconds	1.8
Left vagus acting upon left auricle for 14 seconds	1.9
Left vagus acting upon right auricle for 22 seconds	1.5

Figure 17. Comparing these effects in four steps of 2½ seconds each, with the exception of the left vagus upon the left auricle in which each step equals 2 seconds, one sees from the record that they are very similar to those in the preceding case. The right vagus was very active, having, for both sides of the heart, a latent period of 2 and 3 seconds respectively. The difference in the velocity of the change effected is not so marked in the first 10 seconds as subsequently; yet the difference in the gradient of the activities of the left vagus upon the left and the right auricle is well marked. The latent period of the left vagus, while greater than that of the right, is, comparable to the right vagus, practically the same for both sides of the heart, namely 8 and 9 seconds for the left and right sides respectively. In this experiment the stimulation of the nerves lasted approximately 20 seconds in each case. The deflections from five revolutions of the rheotome were as follows:

	cm.
Right vagus acting upon right auricle	0.9
Right vagus acting upon left auricle	0.7
Left vagus acting upon left auricle	1.0
Left vagus acting upon right auricle	0.6

Figure 18. This is a record of the only instance in this series in which stimulation of the left vagus nerve did not stop the heart beat but caused a progressive slowing of the rate from 30 to 15 beats per minute

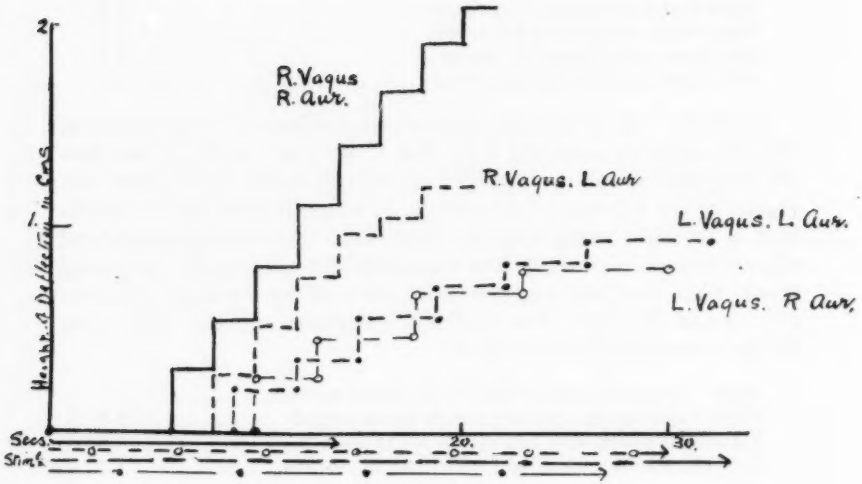
2
R. Vagus
R. Aur.
R. Vagus. L. Aur
L. Vagus. L. Aur.
L. Vagus. R Aur.
Secs
Stim.
20.
30.

Fig. 18

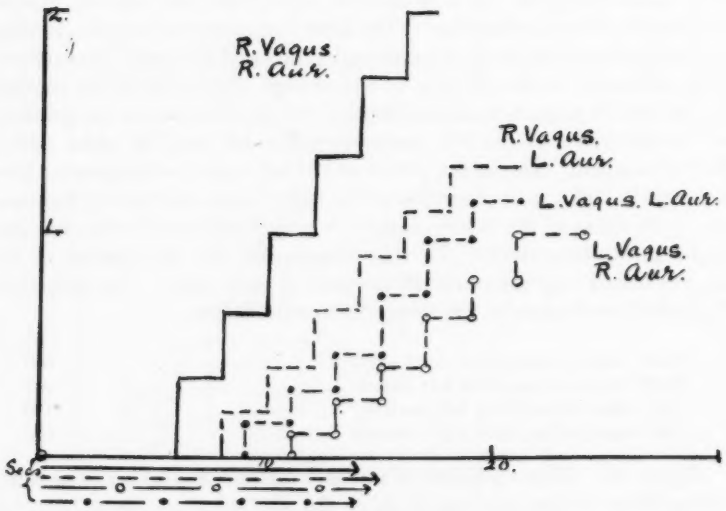
R. Vagus
R. Aur.
R. Vagus.
L. Aur.
L. Vagus. L. Aur.
L. Vagus.
R. Aur.
20.

Fig. 19

in a period of five beats. After the sixth beat there was a pause of 7 seconds, the heart then became tumultuous, big, forcible contractions of the auricles and ventricle, of long duration, following in no regular sequence. After a series of three or four of these had passed, it was again possible to place the galvanometer in circuit with the preparation during the quiescent period, the duration of which became longer and longer till it was again encroached upon by a similar series of irregularly timed, forcible, heaving contractions. While a similar alteration in the rhythm was produced when leading from the right auricle and stimulating the left vagus, the maximal effect was obtained in four steps. The nerve was stimulated for 31 seconds and the maximum reached in 12 seconds. The results for all four activities were as follows:

	cm.
Right vagus acting upon right auricle for 14 seconds	2.1
Right vagus acting upon left auricle for 10 seconds	1.2
Left vagus acting upon left auricle for 32 seconds	1.6
Left vagus acting upon right auricle for 12 seconds	0.8

Figure 19. These curves denote the positive variation obtained with six revolutions of the rheotome, this number being that taken by the smallest curve, left vagus acting upon right auricle, to reach its maximal height.

	cm.
Right vagus acting upon right auricle	2.0
Right vagus acting upon left auricle	1.3
Left vagus acting upon left auricle	1.2
Left vagus acting upon right auricle	1.0

Figure 20. In this case the maximal deflections were recorded step by step with the rheotome revolving once every 2 seconds. The vagi produced complete stoppage of the heart in the times noted on the chart and the deflections were remarkably regular in their rise and bear out what previous records have shown, namely, that the right vagus is the most predominant in action upon the right side of the heart, the left vagus less so on the left side, while here the usually parallel effects of the right vagus upon the left auricle and the left vagus upon its own side, are clearly demonstrated. The deflections for fifteen steps, that is for 30 seconds, were as follows:

	cm.
Right vagus acting upon right auricle	4.5
Right vagus acting upon left auricle	3.6
Left vagus acting upon left auricle	3.6
Right vagus acting upon right auricle	2.7

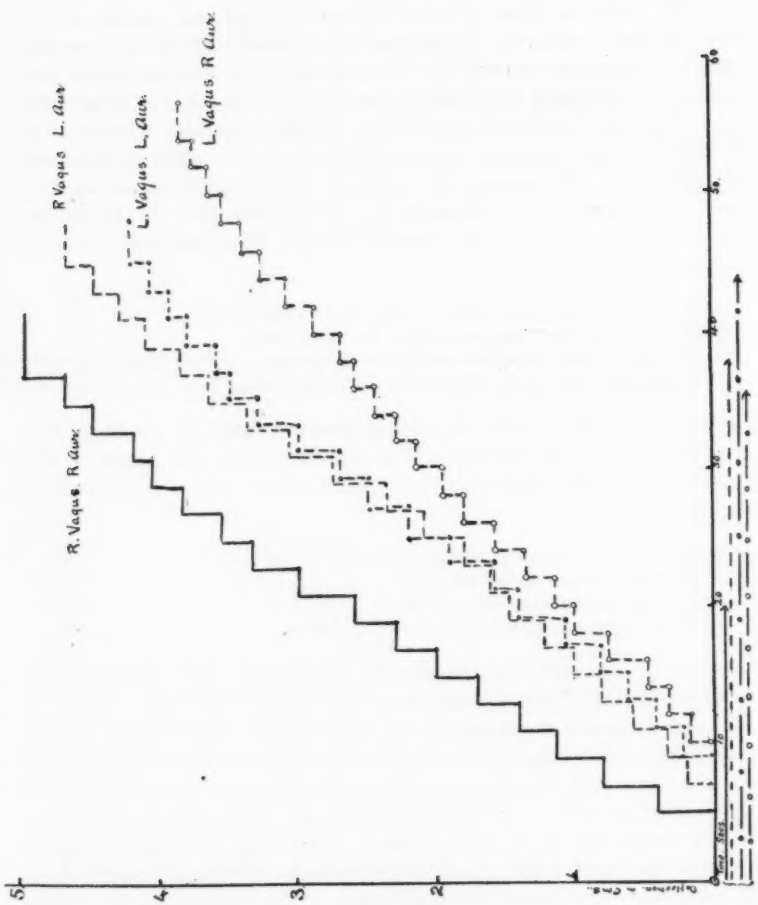

Fig. 20

Results without the rheotome. Figures 21 and 22. These records are given as typical of the curves obtained with a practically quiescent heart, in which deflections caused by electrical changes of weak contractions could be disregarded. These results are from hearts which have been bloodless for from 3 to 4 hours. The curves are plotted for the position of the beam of light every second and the duration of the stimulus is practically 10 seconds in all cases. One again sees the dominant effect of the right vagus, with a latent period of 5 seconds and

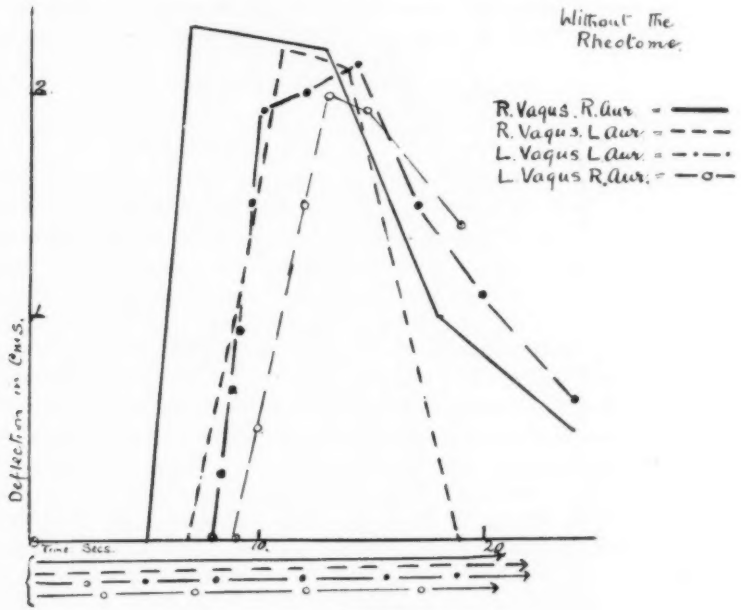

Fig. 21

7 seconds for the respective sides of the heart in both cases. The maximal height is 2.6 cm. and 2.9 cm. respectively. The right vagus effects upon the left auricles are remarkably alike in both cases, the time taken to reach the maximum being 6 and 5 seconds, and the maximal height attained being 2.3 and 2.0 cm., respectively. Such an effect, compared with that obtained from the left vagus acting upon the left auricle, shows the resemblance between the crossed effects of the right vagus and the homolateral effects of the left vagus, with regard to the elec-

trical changes they produce in the left auricle. The rapidity with which the change is produced in the left auricle is greater for the left than for the right vagus. From the latent periods and the heights of the curves, one sees that the crossed effects are slightly less rapid in their inception and in the velocity of their action. It is possible that the

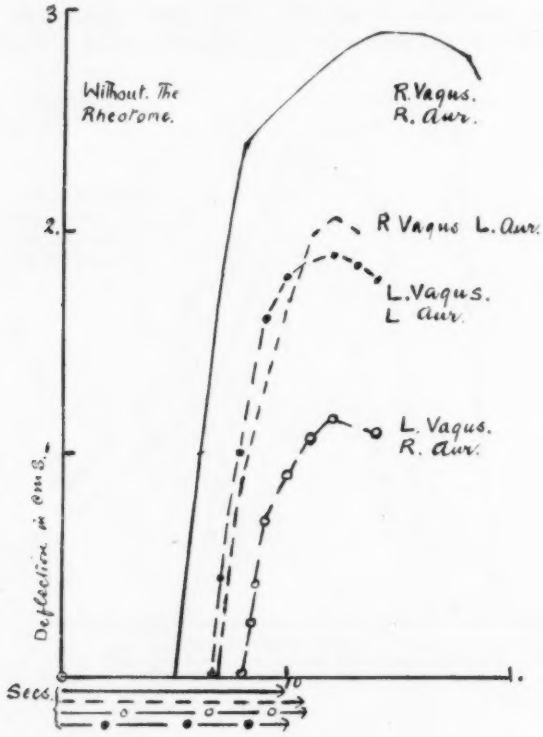

Fig. 22

latent period, in obtaining crossed effects, is directly proportional to the degree of the contralateral distribution of the vagi. From the usually short lapse of time, 1 to 3 seconds, occurring in the production of the crossed effects, either by the right or the left vagus nerves, one must conclude that, anatomically, the crossed distribution of each vagus may, in many instances, be a liberal one.

With regard to the quantitative effects of the vagi upon the whole heart, the results may be summed up in a table of the various effects reduced to a percentage of the sum total:

Right vagus acting upon right auricle	40.9	26.6	35.0	36.3	31.2	30.0
Right vagus acting upon left auricle	20.4	21.9	21.4	23.6	25.0	24.3
Left vagus acting upon left auricle	23.6	30.1	29.5	21.8	25.0	25.7
Left vagus acting upon right auricle	15.0	20.3	14.2	18.1	18.7	20.3

This gives an average result of:

Right vagus acting upon right auricle	30 to 40
Right vagus acting upon left auricle	20 to 25
Left vagus acting upon left auricle	25 to 30
Left vagus acting upon right auricle	15 to 20

DISCUSSION

The experiments carried out with the d'Arsonval galvanometer described in the first part of this paper, corroborate the work of previous investigators with regard to the presence, in the heart muscle, of electrical changes, which are brought about by stimulation of the vagus nerves. It has been shown that these changes can be produced by each vagus nerve acting upon the opposite side of the heart. From the figures quoted in table 1 and from records shown of experiments upon the whole heart, it is evident that the action of the vagi is not mainly homolateral. As far as the vagus effect is distinguished by an increased positivity, by a change in potential, one must conclude that each vagus nerve exerts its greatest effect upon its own side, and upon the opposite side an effect which, generally, is definitely less than, but may, in the case of the right vagus, be almost as great as that of its homolateral action. In comparing the two vagi, it is seen from these results that the right vagus produces a much greater contralateral effect than does the left; that the effect of the right vagus upon the left auricle is generally less than that of the left vagus upon its own side. In only two cases did the left vagus acting upon the right auricle produce an effect greater than that of the homolateral action of the right vagus. It is seen that the contralateral effect of the left vagus is undoubtedly the weakest or least marked of all four activities studied.

These results do not substantiate Garrey's conclusions with regard to the preponderantly homolateral effects of the vagi. There may be a tendency to over-emphasize the homolateral view. In Garrey's case this may have resulted from his assumption that the beat originated

in the right caval vein and from the fact that he could find no chronotropic effects thereon with left vagus stimulation. He states "that the left vagus is less effective upon the normal rhythm of the heart than the right vagus, due to the fact that it does not innervate the right basal vein;" and again he states "that crossed effects can be obtained, in some cases even to chronotropic effects, on the right veins by action of the left vagus."

If the left vagus can affect the center of rhythmicity in the left side of the partially split heart, is it not, from these results and from Garrey's suggestion, justifiable to conclude that the left vagus can or may, as a usual function, affect the pace-maker or center or centers of rhythmicity in the right auricle in the whole heart?

That such may be the case, more or less marked according to the degree of crossed distribution, is strongly suggested by the results recorded above, in which, in almost every case, left vagus stimulation quickly arrested the beat of the heart. As there were no evidences of block one must conclude that this is due to an effect upon the center of rhythmicity and that to stop the heart the vagus must act upon all heart tissue which is inherently rhythmical. Thus only, in those cases of complete stoppage, can left vagus inhibition be explained and this point of view demands a contralateral distribution of both vagi. With regard to the partially split heart, it is shown from the figures in table 2 and from the tracings briefly referred to, that here only are the effects of the vagi strictly confined to their respective sides.

This raises the question of the conduction of crossed effects which, according to Garrey, occurs by means of nerve. In the turtle, the crossed effects obtained in the whole heart must pass to the auricle by way of nerve fibers located in the tissue of the sinus. If the vagus effects were the result of a general conduction by means of both muscle and nerve, then, seeing that the muscle wave spreads around the sagittally split heart from right to left, there should be no reason why the vagus effect should not so pass.

In the partially split heart right vagus stimulation stops the whole initially, then the left sinus assumes a controlling rhythmicity for the left side, and if the right side be maintained in inhibition for some time, the beats originating in the left sinus will travel from left to right, but they will not pass from the ventricle to the right auricle. The passage of such contraction impulses shows that no vagus control is exercised upon the ventricle in the turtle. Also, it must be concluded that in the partially split heart no vagus effects can be transmitted across from

the right to the left side of the heart, since there is no alteration in the electrical potential of the injury current of the left auricle when the right vagus is stimulated.

In concluding that the ventricular muscle of the turtle plays no part in transmitting vagus effects, it must be borne in mind that the reason may not necessarily lie in the ventricular tissue but in the inability of junctional tissue to transmit these effects. That vagus effects do not spread by way of the ventricle would not preclude such spread from right auricle to left auricle through cardiac tissue proper. Erlanger (17) and Erlanger and Hirschfelder (18) have shown that, after clamping the bundle of His in the dog and thereby producing partial or complete heart block, it is possible to demonstrate some action, though slight, of the vagus upon the ventricle. This goes to show that vagal impulses to some extent travel by routes other than those which subserve normal physiological conduction of the cardiac impulses.

That these impulses may not be associated with ordinary nerve fibers is suggested by the work of Meek and Leaper (19), who show that conduction in the heart, either by nerve fiber or by skeletal muscle, manifests no marked difference in the degree of compression necessary to destroy it. Garrey, in a study of the dissociation of inhibitory nerve impulses, states, "that if normal physiological conduction from sinus to auricle proceeds along nervous paths the blocking of these paths should at the same time block other nervous paths, including all vagus fibers which pass to the auricle through the clamped area, and through this area only." He shows that this is not the case; that compression sufficient to establish complete sino-auricular block, may not interfere with the passage of vagus impulses. This would indicate that if vagus effects are to be transmitted they must pass by way of tissue peculiar to them. That such effects do not spread through muscle tissue is proved by the larger effect upon the corresponding side in the whole heart. This rules out the idea that junctional tissue may be the cause of a non-transmittal of these effects in the partially split heart.

From these results one is led to the conclusion that there is no case for the spread of vagus effects by non-specific tissue, either muscular or nervous, but only by tissue hypothetically peculiar to vagus conduction. It would seem, from the results both in the normal and partially split heart, that for crossed effects in the whole heart, it is not a case of strong or weak stimuli affecting muscle fibers or nerve network, but rather a case of stimuli efficient enough to pass along paths of vagus conduction, the degree to which contralateral function is served depending upon the richness of the anatomical distribution.

With regard to the distribution of both vagi, evidence for a rich contralateral supply to the heart is borne out by this work and in support of this view reference has been made to the work of Cohn and of Robinson. The latter investigator showed that in gauging the action of the vagi upon cardiac conductivity, the rate of the heart had to be taken into account. From this it is seen that, in judging both of chronotropic and dromotropic effects of the vagi, the factor of greatest importance is the action of both right and left vagus nerves upon the center or centers of rhythmicity.

If it is assumed that the vagus acts by reducing the general reactivity of the tissue it happens to innervate directly, then the observation frequently recorded in the literature that left vagus stimulation often blocks the transmission of the contraction wave may be accounted for upon the basis of differences in the distribution of the two vagi with respect to the pacemaker. If in a given case the left vagus innervates the whole of the base of the heart excepting the pace-maker while the right vagus acts upon both parts equally, then stimulation of the left vagus will reduce reactivity and consequently the conductivity of the auricles, but not the rate of impulse initiation. The result would simulate the diminution in conductivity. Stimulation of the right vagus would produce the same reduction in reactivity and of the same parts but at the same time would slow impulse initiation. As a result the interval between successive impulse conductions might become long enough to permit the subjacent tissues, despite their lowered reactivity, to carry every impulse that came from the pace-maker. If the beats could be maintained at their original rate while the right vagus was being stimulated, a diminution of conductivity similar to that produced by left vagus stimulation would become manifest.

CONCLUSIONS

It is concluded that the positive variation of the demarcation current that develops during vagus stimulation is a phenomenon, not due to, although usually associated with, stoppage of the heart. This is shown by the facts:

1. That in the quiescent heart the electro-positive change is obtained.
2. That no electro-positive change is obtained, when in the partially split heart the left auricle temporarily stops beating upon right vagus stimulation.

Thus, looking at the question from two totally different standpoints, we have clear evidence that the electrical change indicative of inhibition is not occasioned merely by the cessation of muscle activity.

It is also concluded that in the turtle the distribution of the vagi through the base of the heart is bilateral, but is not uniform in all parts. In general the relative intensity of action is as follows: Right vagus on right auricle > right vagus on left auricle = left vagus on left auricle > left vagus on right auricle.

The greater tendency, noted in the literature, of stimulation of the left vagus to produce block is not necessarily due to a selective action of this nerve upon the conducting system; the result can be explained quite as well through the relatively slight action of the left nerve upon the pace-maker, which is located on the right side of the heart, while the reactivity of the remainder of the heart is reduced.

I am greatly indebted to Doctor Erlanger for his continued interest in this problem, and for much helpful and very suggestive criticism.

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THE INFLUENCE OF GLANDS WITH INTERNAL SECRETIONS ON THE RESPIRATORY EXCHANGE

I. Effect of the Subcutaneous Injection of Adrenalin on Normal and Thyroidectomized Rabbits

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The demonstration by Asher and Flack (1), (2), (3) that stimulation of the laryngeal nerves in rabbits with intact thyroids increases and prolongs the rise in blood pressure following the intravenous injection of a given amount of adrenalin has provided the first concrete evidence of a thyroid-adrenal relationship. The Goetsch (4) test in exophthalmic goiter and in clinical conditions resembling exophthalmic goiter, as tuberculosis, cardiac neuroses, etc., is a practical diagnostic application of Asher and Flack's original observations. The effect of the subcutaneous injection of adrenalin on the respiratory exchange in man was studied in 1912 by Fuchs and Roth (5), who found a slight increase in the oxygen intake and carbon dioxide output which they looked upon as negligible and an increase in the respiratory quotient. Later work by Bernstein (6), by Peabody and his co-workers (7), by Tompkins, Sturgis and Wearn (8) and by Sandiford (9) have clearly established that in normal men adrenalin injected subcutaneously in 0.5 cc. to 1.0 cc. (1–1000) doses causes an increase in the respiratory exchange. The studies of Tompkins, Sturgis and Wearn and of Sandiford are the more recent and extensive. The former, working with soldiers, were able to demonstrate the increase in twenty-seven of thirty-four cases. The latter studied forty-six cases including exophthalmic goiter, simple goiter, myxedema, Addison's disease and four normals. She concludes that the subcutaneous injection of 0.5 cc. 1–1000 adrenalin invariably causes an increase in the oxygen intake and the carbon dioxide output.

La Franca (10), working with dogs, found that phloridzin causes a marked decrease in the respiratory exchange, while adrenalin causes a

marked increase both in the respiratory quotient and in the oxygen consumption. Hari (11) using curarized dogs and injecting adrenalin intraperitoneally observed a decrease in the oxygen consumption and a rise in the respiratory quotient. Lusk and Riche (12), studying the effect of adrenalin on the power of the animal to oxidize glucose, noted an increase in the respiratory exchange in two normal dogs. Wilenko (13) used urethanized rabbits and found no change in the respiratory quotient or the oxygen consumption.

In view of Asher and Flack's observation it has seemed to us of importance to compare the effects of the subcutaneous injection of adrenalin in normal and thyroidectomized animals and also to compare the effect on the same animal before and after thyroidectomy. The results of these experiments are given in the following pages.

Method. Rabbits have been used because it is possible to remove the thyroids without any physical interference with the function of the iind parathyroids and also because accessory thyroid tissue is less common than in dogs, cats or rats. We have used a Haldane (14) apparatus, modified by substituting Williams' absorbers and a motor-driven pump. This apparatus is readily adapted for the use of rabbits and is simple and accurate.

All rabbits were deprived of food for 15 to 16 hours before beginning the experiments. The adrenalin (P. D. Co., 1–1000) was not assayed. The dose was arbitrarily fixed at 0.5 cc. per kilogram. Each experiment consists of an hour period although in most instances the observations were repeated two or more times without interruption. This makes it possible to compare the results by hours or by longer units of time.

This study includes observations on six rabbits which had been kept in the laboratory for several months under the same conditions before being used in this work. Three rabbits (R 3–203, –205, –206) were "normal." Three had had thyroidectomies—one (3–208) 51 days before beginning the studies and two (3–201 and 3–204) during the studies. The detail figures obtained in each of these animals have been arranged in tables 2, 3, 4, 5, 6 and 7. For the brief discussion which follows, only the figures for the O_2 consumption per gram of body weight per hour will be considered. These have been averaged and arranged in table 1.

a. Controls (before administration of adrenalin). The average O_2 consumption for the five rabbits with intact thyroids was 0.607, 0.572, 0.524, 0.477 and 0.436 gram per gram of body weight per hour

before the administration of adrenalin. These figures might be termed the basal rates and show the usual "normal" variations for different animals though the rate is relatively constant for a given animal. Rabbit 3–208 which had been thyroidectomized 51 days before beginning the observation shows the ordinary effect of thyroidectomy on metabolism first described in man by Magnus-Levy (16).

With rabbits 201 and 204 it is possible to compare the O_2 consumption before and after thyroidectomy. The figures given in table 1 represent the first series of observations before thyroidectomy and the last after thyroidectomy (30 and 31 days). The decrease in O_2 consumption following thyroidectomy is striking. Reference to tables 6

TABLE 1

Average O_2 consumption per gram per hour in cubic centimeters

RABBIT NUMBER	CONDITION OF THYROID	CONTROL	FIRST HOUR AFTER 0.5 CC. ADRENALIN PER KILOGRAM	SECOND HOUR AFTER 0.5 CC. ADRENALIN PER KILOGRAM	THIRD HOUR AFTER 0.5 CC. ADRENALIN PER KILOGRAM	FOURTH HOUR AFTER 0.5 CC. ADRENALIN PER KILOGRAM	
203	Intact	0.607	0.637	0.697	0.789	0.680	0.708
205	Intact	0.436	0.528	0.549	0.595		
206	Intact	0.524	0.545	0.605			
208	Thyroidectomy 51 days	0.355	0.344	0.417	0.433	0.457	
204	Intact	0.477	0.651	0.610	0.530		
204	30 days after thyroidectomy	0.348	0.326	0.498	0.366		
201	Intact	0.572	0.530	0.681			
201	31 days after thyroidectomy	0.402	0.396	0.502	0.480		

and 7 show that the decrease in the rate of metabolism following thyroidectomy is very slow—several days being required before the change becomes manifest. This may be due to the fact that the thyroid hormone is very stable and is normally needed in exceedingly small amounts.

These observations are in harmony with the clinical observations that the onset of symptoms of myxedema in thyroidectomized animals is slow and also that there is usually a latent period of 24 to 48 hours following the feeding of desiccated thyroid before an increase in the metabolic rate can be demonstrated. They are at variance with the effects on blood pressure as reported by Asher and Flack (loc. cit.) and by Levy (17). These authors showed that in acute experiments

TABLE 2

Rabbit 3-203. Thyroids intact

EXPERIMENT NUMBER	DATE	WEIGHT	DURATION	O_2 INTAKE	CO_2 OUTPUT	$\frac{CO_2}{O_2}$	O_2 PER GRAM PER HOUR	ADDITIONAL DATA
		grams		*grams*	*grams*		*cc.*	
1	5- 4-20	2125	3:20- 4:20 p.m.	1.570	2.210	1.02	0.516	Normal control
8	5- 6-20	2095	3:10- 4:10 p.m.	1.670	2.090	0.91	0.557	Normal control—1st hour
9	5- 6-20	2095	4:18- 5:18 p.m.	2.000	2.350	0.85	0.667	Normal control—2nd hour
19	5-11-20	2080	10:04-11:04 a.m.	2.170	1.990	0.67	0.729	Normal control—1st hour
20	5-11-20	2080	11:08-12:08 p.m.	2.170	2.090	0.70	0.740	Normal control—2nd hour
34	5-15-20	2025	10:36-11:36 a.m.	1.550	1.790	0.84	0.565	Normal control
36	5-15-20	2025	2:55- 3:55 p.m.	2.000	2.650	0.96	0.690	2:48 p.m. Injected subcutaneously 0.5 cc. adrenalin (P. D. Co. 1:1000) per kilogram
42	5-18-20	2030	9:35-10:35 a.m.	1.620	1.950	0.87	0.558	Normal control—1st hour
43	5-18-20	2030	10:35-11:35 a.m.	1.650	1.680	0.73	0.568	Normal control—2nd hour
44	5-18-20	2025	1:15- 2:15 p.m.	1.860	2.440	0.95	0.642	1st hour following adrenalin injection. 1:05 p.m. Injected subcutaneously 0.5 cc. adrenalin (P. D. Co. 1:1000) per kilogram
45	5-18-20	2025	2:15- 3:15 p.m.	2.330	2.720	0.85	0.804	2nd hour following adrenalin injection
46	5-18-20	2025	3:15- 4:15 p.m.	2.350	2.410	0.75	0.811	3rd hour following adrenalin injection
47	5-18-20	2025	4:15- 5:15 p.m.	1.970	2.300	0.85	0.680	4th hour following adrenalin injection
48	5-18-20	2025	5:15- 6:15 p.m.	2.050	2.140	0.76	0.708	5th hour following adrenalin injection
77	6- 4-20	2100	10:55-11:55 a.m.	1.710	1.870	0.79	0.569	Normal control
78	6- 4-20	2095	1:40- 2:40 p.m.	1.740	2.140	0.89	0.580	1.35 p.m. Injected subcutaneously 1.05 cc. adrenalin (P. D. Co. 1:1000) per kilogram. 1st hour following adrenalin injection
79	6- 4-20	2095	2:40- 3:40 p.m.	1.770	2.110	0.85	0.590	2nd hour following adrenalin injection
80	6- 4-20	2095	3:40- 4:40 p.m.	2.300	2.800	0.88	0.768	3rd hour following adrenalin injection

TABLE 3

Rabbit 3-205. Thyroids intact

EXPERIMENT NUMBER	DATE	WEIGHT	DURATION	O_2 INTAKE	CO_2 OUTPUT	$\frac{CO_2}{O_2}$	O_2 PER GRAM PER HOUR	ADDITIONAL DATA
		grams		*grams*	*grams*		*cc.*	
92	6-11-20	2180	9:30–10:30 a.m.	1.320	1.540	0.85	0.423	Control
93	6-11-20	2180	10:30–11:30 a.m.	1.330	1.370	0.75	0.426	Control
94	6-11-20	2170	2:50– 3:50 p.m.	1.750	2.400	0.99	0.564	2:42 p.m. Injected subcutaneously 0.5 cc. adrenalin (P. D. Co. 1:1000) per kilogram. 1st hour following adrenal injection
104	6-21-20	2135	9:30–10:30 a.m.	1.300	1.390	0.78	0.426	Control
105	6-21-20	2135	10:30–11:30 a.m.	1.440	1.590	0.80	0.471	Control
106	6-21-20	2115	1:40– 2:40 p.m.	1.490	2.090	1.02	0.492	1:31 p.m. Injected subcutaneously 0.5 cc. adrenalin (P. D. Co. 1:1000) per kilogram. 1st hour following adrenalin injection
107	6-21-20	2115	2:50– 3:50 p.m.	1.660	2.210	0.97	0.549	2nd hour following adrenalin injection
108	6-21-20	2115	4:00– 5:00 p.m.	1.800	2.060	0.83	0.595	3rd hour following adrenalin injection

TABLE 4

Rabbit 3–206. Thyroids intact

EXPERIMENT NUMBER	DATE	WEIGHT	DURATION	O_2 INTAKE	CO_2 OUTPUT	$\frac{CO_2}{O_2}$	O_2 PER GRAM PER HOUR	ADDITIONAL DATA
		grams		*grams*	*grams*		*cc.*	
81	6- 4-20	2390	9:45–10:45 a.m.	1.960	1.970	0.73	0.573	Control
82	6- 4-20	2390	10:45–11:45 a.m.	1.610	1.770	0.80	0.471	Control
84	6- 4-20	2380	2:20– 3:20 p.m.	2.050	2.350	0.83	0.602	1:15 p.m. Injected subcutaneously 0.5 cc. adrenalin (P. D. Co. 1:1000) per kilogram
								2nd hour following adrenalin injection
86	6- 4-20	2325	5:01– 6:01 p.m.	2.160	2.030	0.68	0.650	4th hour following adrenalin injection
100	6-19-20	2400	10:05–11:05 a.m.	1.710	2.090	0.89	0.498	Control
101	6-19-20	2400	11:05–12:05 p.m.	1.900	2.080	0.80	0.553	Control
102	6-19-20	2390	2:10– 3:10 p.m.	1.670	2.250	0.98	0.488	2:00 p.m. Injected subcutaneously 0.5 cc. adrenalin (P. D. Co. 1:1000) per kilogram.
								1st hour following adrenalin injection
103	6-19-20	2380	3:40– 4:40 p.m.	2.060	2.920	1.03	0.605	2nd hour following adrenalin injection

TABLE 5

Rabbit 3-208. R. and L. Thyroidectomy 3-22-20

EXPERIMENT NUMBER	DATE	WEIGHT	DURATION	O_2 INTAKE	CO_2 OUTPUT	$\frac{CO_2}{O_2}$	O_2 PER GRAM PER HOUR	ADDITIONAL DATA
		grams		*grams*	*grams*		*cc.*	
24	5-12-20	2445	11:53-12:53 p.m.	1.020	1.140	0.81	0.292	Control
25	5-12-20	2440	2:00- 3:00 p.m.	1.160	1.450	0.91	0.332	1:55 p.m. Injected subcutaneously 0.5 cc. adrenalin (P. D. Co. 1:1000) per kilogram. 1st hour following adrenalin injection
26	5-12-20	2440	3:00- 4:00 p.m.	1.110	1.020	0.67	0.318	2nd hour following adrenalin injection
33	5-14-20	2410	4:35- 5:35 p.m.	1.450	1.590	0.80	0.421	Control
37	5-17-20	2500	10:21-11:21 a.m.	1.530	2.100	1.00	0.428	Control
38	5-17-20	2500	11:21-12:21 p.m.	1.400	1.990	1.03	0.392	Control
39	5-17-20	2495	1:43- 2:43 p.m.	1.390	2.020	1.06	0.393	1:33 p.m. Injected subcutaneously 0.5 cc. adrenalin (P. D. Co. 1:1000) per kilogram. 1st hour following adrenalin injection
40	5-17-20	2495	2:43- 3:43 p.m.	1.510	2.160	1.04	0.423	2nd hour following adrenalin injection
56	5-20-20	2450	9:35-10:35 a.m.	1.320	1.580	0.87	0.377	Control
57	5-20-21	2450	10:35-11:35 a.m.	1.160	1.440	0.90	0.331	Control
58	5-20-20	2450	11:35-12:35 p.m.	1.040	1.350	0.94	0.297	Control
59	5-20-20	2445	2:00- 3:00 p.m.	1.220	1.510	0.90	0.349	1st hour following adrenalin injection. 1:51 p.m. Injected subcutaneously 0.5 cc. adrenalin (P. D. Co. 1:1000) per kilogram
60	5-20-20	2445	3:00- 4:00 p.m.	1.580	1.650	0.76	0.452	2nd hour following adrenalin injection
61	5-20-20	2445	4:00- 5:00 p.m.	1.630	1.680	0.75	0.466	3rd hour following adrenalin injection
115	6-23-20	2530	9:40-10:40 a.m.	1.170	1.680	1.04	0.323	Control
116	6-23-20	2530	10:40-11:40 a.m.	1.220	1.540	0.92	0.337	Control
117	6-23-20	2525	1:20- 2:20 p.m.	1.090	1.590	1.06	0.302	1:16 p.m. Injected subcutaneously 0.5 cc. adrenalin (P. D. Co. 1:1000) per kilogram. 1st hour following adrenalin injection
118	6-23-20	2525	2:20- 3:20 p.m.	1.720	2.090	0.88	0.476	2nd hour following adrenalin injection
119	6-23-20	2525	3:20- 4:20 p.m.	1.450	1.680	0.84	0.401	3rd hour following adrenalin injection
120	6-23-20	2525	4:20- 5:20 p.m.	1.650	1.660	0.73	0.457	4th hour following adrenalin injection

TABLE 6

Rabbit 3-204. Thyroidectomy 5-21-20

EXPERIMENT NUMBER	DATE	WEIGHT	DURATION	O_2 INTAKE	CO_2 OUTPUT	$\frac{CO_2}{O_2}$	O_2 PER GRAM PER HOUR	ADDITIONAL DATA
		grams		*grams*	*grams*		*cc.*	
49	5-19-20	2425	9:22-10:22 a.m.	1.710	1.960	0.83	0.493	Control
50	5-19-20	2425	10:22-11:22 a.m.	1.600	1.840	0.84	0.461	Control
52	5-19-20	2375	1:40- 2:40 p.m.	2.210	2.680	0.88	0.651	1:33 p.m. Injected subcutaneously 0.5 cc. adrenalin (P. D. Co. 1:1000) per kilogram. 1st hour following adrenalin injection
53	5-19-20	2375	2:40- 3:40 p.m.	2.070	2.690	0.94	0.610	2nd hour following adrenalin injection
54	5-19-20	2375	3:40- 4:40 p.m.	1.800	2.240	0.90	0.530	3rd hour following adrenalin injection
66	5-24-20	2330	10:10-11:10 a.m.	1.500	1.750	0.85	0.450	Removed most of R. and L. thyroid lobes 5-21-20. Control
67	5-24-20	2330	11:10-12:10 a.m.	1.830	1.840	0.82	0.549	Control
68	5-24-20	2225	1:55- 2:55 p.m.	1.300	1.660	0.93	0.409	1:46 p.m. Injected subcutaneously 0.5 cc. adrenalin (P. D. Co. 1:1000) per kilogram. 1st hour following adrenalin injection
69	5-24-20	2225	2:55- 3:55 p.m.	1.690	2.110	0.91	0.531	2nd hour following adrenalin injection
70	5-24-20	2225	3:55- 4:55 p.m.	2.030	2.010	0.72	0.638	3rd hour following adrenalin injection
71	6- 2-20	2400	9:20-10:20 a.m.	1.180	1.370	0.84	0.344	Control
73	6- 2-20	2400	1:50- 2:50 p.m.	1.220	1.860	1.11	0.355	1:15 p.m. Injected subcutaneously 0.5 cc. adrenalin (P. D. Co. 1:1000) per kilogram. 1st hour following adrenalin injection
74	6- 2-20	2400	2:50- 3:50 p.m.	1.420	1.770	0.91	0.414	2nd hour following adrenalin injection
75	6- 2-20	2400	3:50- 4:50 p.m.	1.390	1.680	0.88	0.405	3rd hour following adrenalin injection
96	6-18-20	2490	10:55-11:55 a.m.	1.240	1.540	0.90	0.348	Control
97	6-18-20	2485	2:05- 3:05 p.m.	1.160	1.630	1.02	0.326	1:57 p.m. Injected subcutaneously 0.5 cc. adrenalin (P. D. Co. 1:1000) per kilogram. 1st hour following adrenalin injection
98	6-18-20	2485	3:05- 4:05 p.m.	1.770	2.010	0.83	0.498	2nd hour following adrenalin injection
99	6-18-20	2485	4:05- 5:05 p.m.	1.300	1.710	0.91	0.366	3rd hour following adrenalin injection

TABLE 7

Rabbit 3-201. Thyroidectomy 5-21-20

EXPERIMENT NUMBER	DATE	WEIGHT	DURATION	O_2 INTAKE	CO_2 OUTPUT	$\frac{CO_2}{O_2}$	O_2 PER GRAM PER HOUR	ADDITIONAL DATA
		grams		*grams*	*grams*		*cc.*	
62	5-22-20	2360	3:15- 4:15 p.m.	1.960	2.000	0.74	0.581	Control
63	5-22-20	2360	4:15- 5:15 p.m.	1.900	1.830	0.70	0.563	Control
64	5-22-20	2360	5:30- 6:30 p.m.	1.790	2.530	1.03	0.530	5:19 p.m. Injected subcutaneously 0.5 cc. adrenalin (P. D. Co. 1:1000) per kilogram; 1st hour following adrenalin injection
65	5-22-20	2360	6:30- 7:30 p.m.	2.300	2.320	0.73	0.681	2nd hour following adrenalin injection
87	6-10-20	2840	9:20-10:20 a.m.	1.460	1.950	0.97	0.359	Control
88	6-10-20	2840	10:20-11:20 a.m.	1.170	1.480	0.92	0.295	Control
89	6-10-20	2825	1:50- 2:50 p.m.	1.340	2.290	1.33	0.332	1:45 p.m. Injected subcutaneously 0.5 cc. adrenalin (P. D. Co. 1:1000) per kilogram urinated in chamber. 1st hour following adrenalin injection
91	6-10-20	2825	4:15- 5:15 p.m.	2.020	2.230	0.81	0.513	3rd hour following adrenalin injection
109	6-22-20	2860	9:20-10:20 a.m.	1.750	2.230	0.93	0.428	Control
110	6-22-20	2860	10:20-11:20 a.m.	1.550	1.850	0.87	0.386	Control
111	6-22-20	2860	11:35-12:35 p.m.	1.610	2.130	1.10	0.394	Control
112	6-22-20	2840	2:00- 3:00 p.m.	1.610	2.470	1.11	0.396	1:54 p.m. Injected subcutaneously 0.5 cc. adrenalin (P. D. Co. 1:1000) per kilogram. 1st hour following adrenalin injection
113	6-22-20	2840	3:10- 4:10 p.m.	2.040	2.650	0.94	0.502	2nd hour following adrenalin injection
114	6-22-20	2840	4:21- 5:21 p.m.	1.950	2.300	0.86	0.480	3rd hour following adrenalin injection

lasting only a few hours the effect of adrenalin on blood pressure was markedly decreased by thyroidectomy. The cause of these time differences between the effect of adrenalin on blood pressure and on metabolism in animals with and without thyroidectomy is not clear.

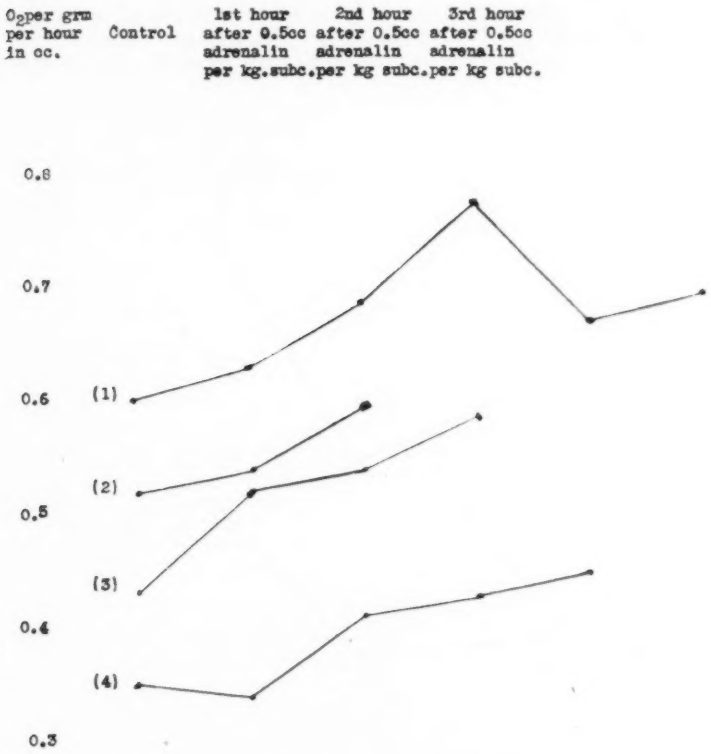

Fig. 1. Average O_2 consumption per gram per hour in cubic centimeters. *1*, Rabbit 203, thyroids intact; *2*, rabbit 206, thyroids intact; *3*, rabbit 205, thyroids intact; *4*, rabbit 208, thyroids removed (51 days).

b. After adrenalin administration. In each case 0.5 cc. per kgm. (P. D. adrenalin 1–1000) unassayed stock adrenalin was injected subcutaneously in the flank. The observations were recorded in hourly periods following the injection. In all instances a rise in the O_2 consumption was noted. The changes are shown graphically in text fig-

ures 1, 2 and 3. It occurs as well in the thyroidectomized animals as in "normals." This is brought out best in figures 2 and 3 when the effect of adrenalin before and after thyroidectomy may be compared in

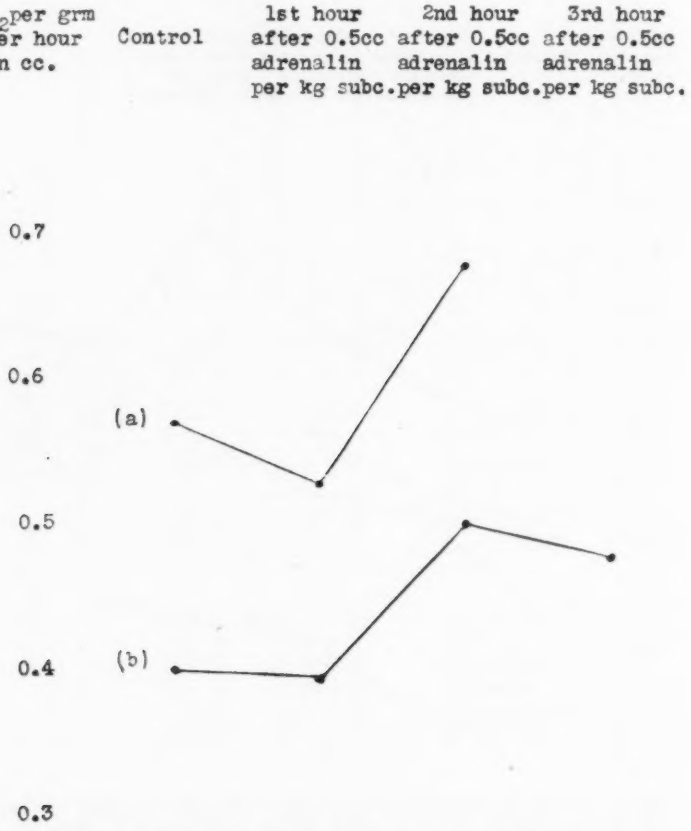

Fig. 2. Rabbit 201. Average O_2 consumption per gram per hour in cubic centimeters. *a*, Thyroids intact; *b*, thyroids removed (31 days).

the same animal. The percentile rise in O_2 consumption appears to be little changed by thyroidectomy. These results confirm Sandiford's observations in human myxedema. The adrenalin effect lasts for hours. We have observed it for five hours, though usually the great-

est increase is reached in the third hour. There is some evidence that in the thyroidectomized animals the onset of the increased rate of metabolism is delayed and also the reaction is of shorter duration as

O_2 per grm per hour in cc.	Control	1st hour after 0.5cc adrenalin per kg.subc.	2nd hour after 0.5cc adrenalin per kg subc.	3rd hour after 0.5cc adrenalin per kg.subc.

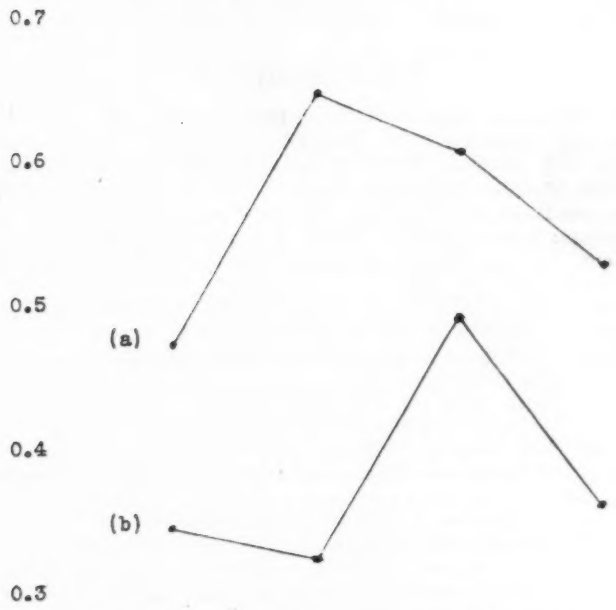

Fig. 3. Rabbit 204. Average O_2 consumption per gram per hour in cubic centimeters. *a*, Thyroids intact; *b*, thyroids removed (30 days).

shown in figures 2 and 3. Another observation on the effect of adrenalin in thyroidectomized animals is that frequently there is a decrease in O_2 consumption during the first hour after adrenalin. This was also observed in "normals" but very rarely.

SUMMARY

Our results on rabbits confirm those of Sandiford on man. Adrenalin causes a rise in the oxygen consumption both in normal and thyroidectomized rabbits. The absolute rise may be greater in normals but the percentile rise may not be altered. Evidence is given that in general the onset of the rise in O_2 consumption following adrenalin is delayed in thyroidectomized animals and also that it does not last so long. Some evidence is presented showing that in rabbits as in other animals the decrease in the metabolic rate following thyroidectomy is gradual and requires several days for its demonstration. These results differ from those in which the effect on blood pressure was used as the indicator.

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STUDIES ON THE VISCERAL SENSORY NERVOUS SYSTEM

III. Lung Automatism and Lung Reflexes in Reptilia (Turtles: Chrysemys elegans and Malacoclemmys lesueurii. Snake: Eutenia elegans)

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LITERATURE

The first observations on the contractility of the reptilian lung on direct stimulation of the pulmonary tissue was made by Paul Bert (1). He showed furthermore that the musculature of the lung was under the motor control of the vagus nerve. These findings have been abundantly corroborated by the subsequent researches of various investigators of whom François-Franck (2) deserves particular mention.[1] Francois-Franck (3), (4) published a number of papers dealing with the comparative physiology of the reptilian lung. The results of these studies are incorporated in two monographs which as far as they touch our work are the most comprehensive and important contributions on the subject. In most forms the vagus is found to exercise a motor control over the lung of the same side. In one lizard (lézard ocelle) the lungs possess in part a crossed innervation the vagus exercising not

[1] Some 32 years after the original observations of Bert, Maar (Skand. Arch. f. Physiol., 1902, xiii, 269) published an article on the gaseous exchange in the lungs of turtles following ligation and stimulation of the vagi and sympathetic nerves under various experimental conditions. This author apparently was not familiar with the fact that the lungs of the turtle are muscular organs innervated through motor fibers carried by the vagus. The possibility that changes in gaseous exchange (increased oxygen consumption and increased CO_2 following ligation of the vagus) might be accounted for by contraction of the lung (mechanical stimulation of motor fibers) never occurred to this investigator. Practically all positive findings which he attributes to section and stimulation of fibers having a secretory or inhibitory effect on gaseous exchange might be explained by the activity or inactivity of the lung musculature and the passive influence of the circulation through the lungs.

only a homolateral but also a contralateral control over the lungs. François-Franck (5) states that the vagi and not the sympathetic nerves contain the motor fibers for the lungs. Jackson and Pelz (7), on the other hand, state that stimulation of the sympathetic in the neck region with a weak current causes dilatation of the lung and that stronger currents may give a contraction even more promptly and vigorously than stimulation of the vagus itself. In some preparations François-Franck (4), (5) found that electrical stimulation of the vagus in the neck gave rise to a contraction which was preceded by an inhibition. According to his experimental analysis this inhibition is only apparent. He attributes it to a movement of neck muscles. If the muscles of the neck were not involved during peripheral stimulation of the vagus no inhibition preceded the contractions. Personally, we have never obtained an inhibition of the lung on direct stimulation of the peripheral vagus. We have, however, in innumerable instances observed an inhibition preceding lung contractions of central origin. We shall return to this point later in a discussion of this phenomenon.

Kahn (8) and François-Franck (5) have described and pictured rhythmical contractions of the lung due to central discharges from the bulbar nuclei; for they stopped on section of the vagi. Kahn in his analysis on turtles which had suffered high spinal transection showed that these lung contractions followed the external respiratory act; François-Franck noted these rhythmical undulations in the intrapulmonic pressure even in curarized animals but only when the bulbar centers and the vagi were intact. He was never able to obtain a tonus rhythm in any lung separated from its center. He found on electrical stimulation of the peripheral end of the vagus that a secondary contraction may appear on the completion of first; or if the peripheral vagus was tetanized for some time a series of contractions might appear during the period of tetanization simulating tonus variation of the lung. In both instances, however, he was probably dealing with incomplete tetany of the lung rather than with discharges from a peripheral nervous automatic mechanism as a result of the vagus stimulation.

A tonus rhythm appearing in a lung whose extrinsic nerves have been cut would suggest a peripheral nervous mechanism possessing automatic activity. On the anatomical side we have the observations of Leydig (9) and Schulze (10) that the lungs of some turtles possess not only ganglionic swellings on the course of the nerve fibers but actual accumulations of ganglion cells. On the physiological side Fano and Fasola (2) have asserted that the oscillations of tonicity in the lungs of the

turtle, Emys europaea, persist after complete isolation of the lungs from their nervous center although they admit that under normal conditions part of the tonicity is due to impulses reaching the lung through their extrinsic nerves. Since such a peripheral automatism of the lung did not reveal itself in the turtle studied by François-Franck (tortue grecque) and only occasionally in our own preparations it would seem that the question of a peripheral automatic mechanism in the lung may depend on the species as well as on the physiological condition of the animal under observation.

The published reports of lung contractions as a result of the stimulation of various afferent nerves in the reptilia are very meager. Certainly François-Franck, who made a most extensive study of the physiology of the reptilian lung, refers only incidentally to rhythmical lung contractions set up by stimulation of afferent fibers carried by the vagi (3). In his second monograph (4) on the lizard (lézard ocelle) he describes a similar contraction of one lung following ligation of the vagus of the opposite side (mechanical stimulation). Since in this preparation there was intercommunication between the lungs and since he showed that in this species of reptiles the vagus contained motor fibers not only for the lung of the same side but also for the lung of the opposite side, it is possible to explain his supposed reflex contraction on ligation of the vagus nerve to direct motor effects on the opposite lung or to the passive distention of the lung of the opposite side of ligation of the vagus. Both factors would give a record which might be interpreted as an active reflex contraction of the opposite lung.

Prevost and Saloz (10) are the only investigators who, by a method inferior to our own, have described reflex contractions of the lungs of the turtle (tortue grecque). They found that trauma to the carapace, mechanical stimulation of feet, tail, neck and anal region, caused marked contractions of the lungs.

Coombs (12) has recently shown that stimulation of the optic lobes or the medulla in the turtle induced contractions in the lung, provided the vagi are intact. This seems to indicate that the motor innervation to the lungs passes exclusively by the vagi nerves, unless the sympathetic nerves were sectioned by her method of lung isolation.

EXPERIMENTAL PROCEDURE

The solution of the problems under investigation required an accurate recording of the lung tonus and lung contractions with the least possible injury to or interference with the normal respiration and other processes

of the animal. In other words, the necessary aim and requirement so far as possible was to secure *physiological experiments.*

1. Preparation of the animal. No anesthetics were used. Prior (1 to 24 hours) to any dissection or other procedures that would cause pain, the animals were decerebrated by quickly drilling through the skull a little to the side of the median line, introducing a suitable probe through this opening and after cutting off the cerebrum from the midbrain by the transverse stroke virtually pithing the former. By using a small drill and going 2 to 4 mm. lateral to the median line, the median sinus is left intact and profuse hemorrhage avoided. By our method of pithing the cerebrum very little hemorrhage was produced, so that from this factor alone there was little or no impairment to the general circulation or interference with the blood supply of the medulla and midbrain. A small iron hook was introduced into the trephine hole in the skull, by means of which the head was secured to the post as shown in figure 1. The hook being placed in an insensitive spot, the head and neck were thus fixed without the complications from continued irritation of clamps or ligatures about head and neck.

By means of a small drill, holes were made near the edge of the plastron anteriorly and posteriorly, and by strings through these holes in the ventral plate the animal was secured on the turtle stand in the manner shown in figure 1. In the species of turtles worked on, there is a sufficient margin of the ventral plate at both ends for drilling the hole and securing the animal on the stand in its normal posture without touching or injuring the skin.

A few animals were worked on without decerebration. In this case the spinal cord was transected in the neck before any operations were undertaken on the body of the animal.

For convenience of dissection the turtle stand with the animal attached was turned upside down and held in that position by a suitable support while the trachea, the carotids, the jugular vein, the cervical sympathetics, etc., were isolated, balloons introduced into the stomach (via esophagus) and the cannulae and other devices placed in position in the neck and anterior thoracic region.

Isolation of the lungs and other viscera was made by removal of the necessary regions of the dorsal carapace. Cutting through and removing parts of the dorsal carapace is attended with considerable hemorrhage unless care is taken not to injure the intercostal arteries and veins when the calcareous part of the body wall is sawed through or clipped off with strong bone forceps. If suitable care is exercised in this regard,

the diploic veins controlled by surgical wax and the intercostal vessels ligated before cutting away the peritoneum and other structures that adhere closely to the calcareous part, the entire body cavity can be laid open from the dorsal side, with very little immediate and with no chronic hemorrhage.

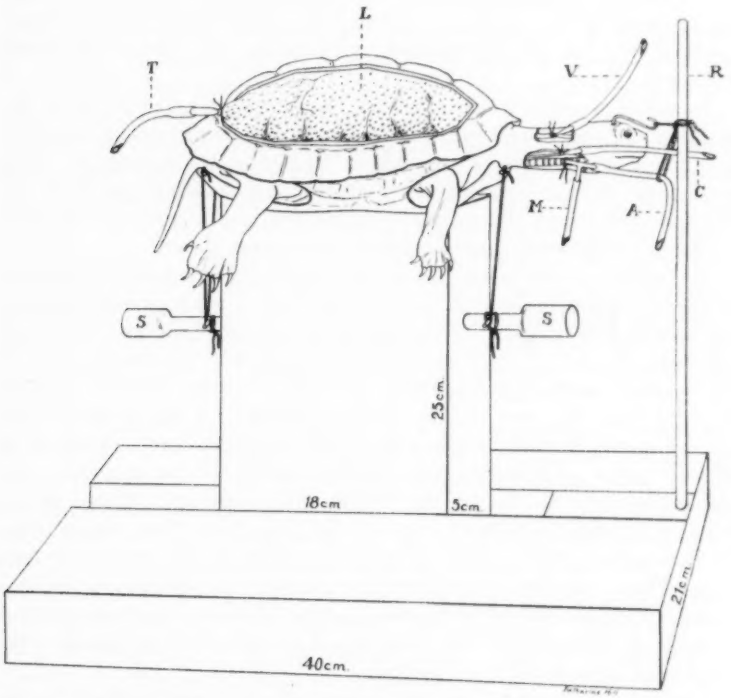

Fig. 1. Diagram of preparation and fixation of the turtle for recording lung contractions. *A:* tube to T-tracheal cannula for spontaneous or artificial respiration in the intact lung. *C:* Cannula in the carotid artery for recording the blood pressure and heart activity. *L:* Lung, isolated, except for pulmonary vagi and blood vessels, bronchus ligated off. Inflated in its normal position in the body cavity. *M:* Tube to manometer for recording the spontaneous respirations. *R:* Flexible steel rod for fixation of the head. *S:* Screws for the fixation of turtle to the top of stand by strings through holes in the plastron. *T:* Cannula and rubber tubing from tip of isolated lung to recording tambour. *V:* Cannula in the jugular vein for intravenous injections.

In a few experiments where it was desired to avoid the injury to visceral sensory nerve connections involved in isolating one lung from the dorsal side, the lungs were exposed and isolated by fixing the animal dorsal side down, removing the entire plastron and dissecting away the liver and greater part of the gut in the way described by Jackson and Pelz (7). In animals fixed on the dorsal side and plastron removed the circulation fails much sooner than if the animal is fixed in the normal position and the viscera exposed by removing one side of the dorsal carapace.

In all our preparations exposing the lungs and viscera from the dorsal side, the dorsal carapace was left intact along the vertebral column, a strip 1 to 1½ cm. wide. This precaution, together with reasonable care in isolating the lung from its attachments along the median line, leaves the main central connections of the visceral sympathetic nerves, except possible fibers to the lung, intact.

2. Isolation of the lung. As is well known, the lung of the turtle is a bilobed organ, united by the two long (3 to 5 cm.) bronchi with the very elongated trachea. The lungs are exceptionally large in comparison with the size of the animal, filling the dorso-lateral region down to the pseudo-diaphragm separating the pelvic cavity and the urinary bladder from the rest of the viscera. Except for the posterior end (about one-sixth of the entire area) the lungs are so firmly attached by fibrous septa and membranes, dorso-laterally to the carapace, and ventro-medially to the visceral organs, that complete collapse of the lungs is impossible without severing the lungs from these connections. It is therefore obvious that accurate recording of lung tonus and lung contractions requires either complete anatomical isolation of the lung from structures whose contractions could influence the lung volume, directly or indirectly, or else complete curarization of the animal. We used both procedures.

Complete isolation of one lung, usually the left, was produced in the following way. The animal being decerebrated, fixed on the turtle stand, as described above, the dorsal carapace over the lung was removed, all the septa and membranes suspending the lung in the body cavity were severed, care being taken not to injure the bronchus, or the pulmonary vagi and blood vessels entering the lungs along the bronchus. In this dissection the lung was not handled directly with forceps or other instruments. It was handled by means of the many membranes and tendons attached to it. It is not necessary to remove these structures close to the lung surface since they can have no effect

on the lung tonus and lung contractions after being severed from their normal connections with the rest of the body. This applies even to the large flattened striated muscle closely adherent and attached to the anterior end of the lung. Directed median- and antero-laterally over the dorsal lung wall and being innervated by fibers from the brachial nerve plexus, the contraction of this muscle reduces the size of the lung cavity and thus serves as a muscle of expiration (fig. 24), supplementing the expiratory muscles of the flank and the walls of the body cavity. This muscle is probably identical with the one described by Fano and Fasola as occurring in Emys europaea (2).

This operation and isolation of the left lung does not cause collapse of the right lung or vice versa. There is naturally some interference with the adequate ventilation in the lung of the intact side by the lowering of the intra-abdominal pressure and the incapacitation of the respiratory flank muscles on the side of the operation, but the animal is usually capable of filling and emptying the lung on the intact side to meet the respiratory needs of the body, especially if one takes care not to puncture the delicate septa partially separating the left and the right side body cavities along the line of the great retractor muscle of the neck.

In figure 2 are shown by diagram the main vago-sympathetic nerve connections. The pulmonary vagi branches, usually two or more in number, are of sufficient size and length to be easily handled for experimental purposes; and the bronchus may be ligated and cannulated without injury to the pulmonary nerves or vessels, and the pulmonary vessels may be ligated or cannulated without injury to the nerves.

There is a persistent tendency on the part of some anatomists and zoölogists, as well as physiologists, to speak of the "bronchioles" or bronchial musculature of the turtle's lung. This is entirely misleading. In species of turtles worked on by us the bronchus terminates peripherally, not by the mode of branching into smaller and smaller divisions (bronchioles), but abruptly in the general lung cavity. We are told by the anatomists that the numerous septa subdividing the lung cavity into irregular chambers have strands of smooth muscle fibers like the external walls of the lungs. But the smallest passages between these chambers are of larger diameter than the trachea itself. These passages and septa are alveolated. If these internal septa and irregular passages are to be termed "bronchioles" on the basis of their musculature, the entire lung of the turtle is composed of "bronchioles." These subdivisions in the turtle lungs are alveolar spaces and not part of the dead space similar to the mammalian bronchioles.

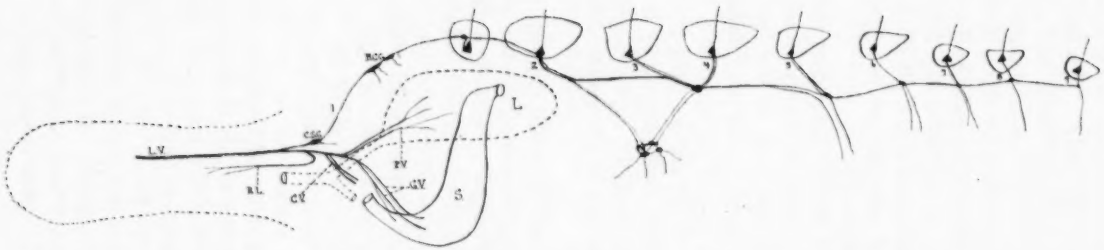

Fig. 2. Diagram of the vago-sympathetic nervous system (left side, ventral view) of the turtle. The diagram of the sympathetic system is not completed posteriorly (sacral region). *L:* Left lung (greatly reduced). *S:* Stomach. *L.V.:* Left vagus. *R.L.:* Recurrent laryngeal nerve. *C.V.:* Cardiac vagi branches. *G.V.:* Gastric vagi branches. *P.V.:* Pulmonary vagi branches. *C.S.G.:* Cervical sympathetic ganglion. *B.S.G.:* Sympathetic ganglia in close association with the brachial nerve plexus. *1:* Cervical sympathetic nerve. *2* to *9:* Nerve connections from the spinal ganglia to the peripheral sympathetic ganglia and nerve plexuses.

3. Recording of the lung contractions. The lung contractions were recorded graphically by water manometers or delicate tambours through air transmission in either case, suitable cannulae being tied either into the bronchus or the free end (posterior tip) of the isolated lung, the isolated lung being distended with air to a pressure of $1\frac{1}{2}$ to 3 cm. of water. In such a preparation active voluntary respiration in the lung on the intact side will still cause passive changes in the intrapulmonic pressure in the isolated lung through the movements of the viscera (on which the isolated and inflated lung rests) especially as a result of very vigorous expiratory movements. We eliminated this source of error in two ways. The isolated and inflated lung was suspended outside the body cavity without traction on the pulmonary nerves or interference with the lung circulation. Or a metal plate was adjusted to the body cavity on the operated side, fixed rigidly to the cut edge of the carapace, except anteriorly, and the isolated and inflated lung placed on this rigid floor, where visceral movements could not influence it. This method can be adjusted so as not to cause traction on the pulmonary nerves, or interference with the pulmonary circulation. The best, and possibly the most physiological method of eliminating these passive lung factors, is partial curarization, that is, doses of curare that will completely paralyze the skeletal muscles, but leave the muscles of respiration largely intact. In our animals this dose varied from $\frac{1}{8}$ to $\frac{1}{4}$ cc. of 1 per cent solution of curare injected intravenously. Turtles subjected to these doses of curare go on breathing regularly though not vigorously, leg and neck movements are abolished, and the gentle respiratory movements on the intact side either do not mechanically influence the isolated and inflated lung on the operated side at all, or else this passive influence is regular or so slight that it is no source of error in the work.

When all these dissections were completed and connections for recording made, the dorsal opening in the carapace was covered with a thick layer of cotton moistened in Ringer's solution, except during such phases of the work as required direct inspection of or working with the isolated lung or its local nerve and blood supply.

4. Artificial respiration. In all cases of complete curarization, artificial respiration was carried out periodically, usually in the intact lung. For that purpose a T-cannula was usually inserted in the trachea. This tracheal cannula was also used in studying the reflex influences of pressure changes in the intact on the isolated lung. The venosity of the blood in the isolated lung was a satisfactory criterion of the need

of artificial respiration. Needless to say, artificial respiration was also resorted to in the animals not curarized, if it appeared that the spontaneous respiration through the lung on the intact side did not suffice to avert asphyxia.

It is well known that the reptilia execute the same buccal respiratory movements as the amphibia, although actual swallowing of the air into the lungs does not occur. However, in labored respiration as in mild or severe asphyxia, the reptilia carry on actual swallowing movements as a part of the respiratory act. These swallowing movements may thus be used as an index of external respiration, or rather attempt at external respiration, in animals with the respiratory muscles immobilized by transection or pithing of the spinal cord.

5. Maintenance of efficient circulation. If we start with an animal vigorous and in good condition, and care is taken to avoid all but the minimum hemorrhage in the experimental procedures, a good circulation will be maintained as shown by direct blood pressure records or by direct inspection of the isolated lung, for 12 to 24 hours or even longer. In feeble animals the circulation fails much earlier. The circulatory failure is due, not to the failure of the heart, but to low blood pressure evidently due to *transudation of the blood plasma into the lymph and tissue spaces.* This is not ordinary oozing of blood from cut surfaces or hemorrhage due to injured vessels. In a turtle preparation in this condition intravenous injection of Ringer's solution improves the circulation only temporarily, the added fluid soon passes out of the blood vessels into the lymph and tissue spaces, and repeated Ringer's solution injections then render the preparation more edematous.

It is not unlikely that this phenomenon is analogous to the passage of plasma from the blood to the tissues in traumatic shock in mammals, as reported by some investigators.

6. Additional preparations of the animal for studying some of the lung reflexes. The turtle preparation described above requires no additional dissection for the study of the lung reflexes induced by inflation or deflation of the intact lung, stimulation of the nares, the cloaca, the penis, the skin or the skeletal nerves. It is even possible by careful manipulation to get at and stimulate the bladder, the rectum, ureter, large and small intestine, etc., through the opening in the dorsal carapace made for the isolation of the lung, without altering the tension on the lung wall mechanically. In the artificial stimulation of the central end of the pulmonary, gastric and vagi branches on the side opposite to the lung under observation it is usually necessary to make

a small opening in the dorsal carapace on that side and partially collapse the intact lung. In the same way inflation of the urinary bladder or the rectum, direct stimulation of the gall bladder, stomach, etc., requires an opening of the carapace posteriorly on the side opposite to the lung under observation, if one is to avoid mechanical errors.

7. On the basis of our own results, and with due regard to methods used by previous investigators on various phases of reptilian respiratory physiology, we feel that a turtle prepared as above with minimum trauma, fixed in normal position without trauma, one lung isolated for accurate observation, the other intact and used in normal spontaneous respiration, is as near its normal physiological state as the necessities of the problem permit. Most phases of lung physiology in the turtle cannot be satisfactorily studied with the animal fixed with the dorsal side down, owing to the special anatomical conditions.

The serious and unavoidable difficulties, apart from that of a laboratory located in a city obtaining turtles in prime condition, are *a*, depressor effects or "central shock" due to sensory effects involved in the operative trauma; *b*, "peripheral shock" or gradual failure of the circulation due to passage of the blood plasma out of the blood vessels into lymph and tissue spaces. It is generally held that reptiles show little or no spinal or traumatic shock, and this was our main reason, besides that of avoiding anesthesia, for working out the visceral reflexes first in this form. Shock, spinal and general, may be minimal but is certainly not absent in the turtle.

8. *Experimental procedure on the snake.* No satisfactory work on the contraction of the lung in these animals can be done without virtually removing the lung from the body, complete pithing of the spinal cord, or complete curarization, thus immobilizing the body. Curarization is, of course, not applicable in experiments on the relation of the lung contractions to the external respiratory act. Hence we used the method of complete pithing of the spinal cord after transection of the cord two or three segments below the medulla. The animal was then fixed, dorsal side down, the lung exposed and isolated by a ventral median incision, taking care to avoid hemorrhage. The recording cannula was inserted in the tip of the lung rather than in the trachea. The trachea was ligated after isolation from the vagi and the neck blood vessels. This preparation is suited only for studying the relation of the respiratory movements to the lung contractions, the vagi action on the lungs, and the lung reflexes evoked from the head region of the animal. In the pithed snake the external respiratory movements appear in the form of attempts at swallowing air just as in the turtle.

In the species of snake used by us the lung is not a paired organ. Alveoli and septa are present in the anterior third of the lung only, the posterior two-thirds of the lung being a delicate apparently muscular sac very much like the primitive lung of necturus. There being only one lung, the necessary artificial respiration had to be carried out periodically in the lung while suspending the recording. This fact renders the snake much less suitable than the turtle for the study of lung motor physiology.

The musculature of the snake lung is very much less developed than that of the turtle. Even delicate water manometers are not sufficiently sensitive for recording the lung contractions. The snake preparations also deteriorate very much faster than does the turtle. Because of these several handicaps the work on the snake was only carried to the point of establishing the identity of the fundamental facts of lung motor physiology in these two groups.

THE RHYTHMIC CONTRACTIONS OF THE LUNGS DURING NORMAL RESPIRATION AND AFTER PARTIAL AND COMPLETE CURARIZATION

1. Typical records of the active lung contractions that follow each external respiratory act or a group of respirations are reproduced in

Fig. 3. Water manometer tracings of the intrapulmonic pressure in the turtle. Animals decerebrated. *A:* Record from left lung; dorsal shell removed on left side, lung isolated except nerve and blood vessel connections. Cannula in left bronchus. The spontaneous respiratory movements at *a* passively influencing the isolated lung. Each group of respiratory movements is followed by contraction of the isolated lung. *B:* Tracing from the same animal as in *A*, 24 hours later after recovery from curare. Record from the intact (right) lung. Cannula in trachea. Each group of respirations is followed by contraction of the lung. *C:* Tracing from left lung, isolated as in *A*, after intravenous injection of a dose of curare (¼ cc. of 1 per cent, to paralyze skeletal muscles). Signal equals gasping or swallowing movements. These are followed by lung contractions. *D: c*, left lung isolated as in *A; b*, right lung in normal attachments. *a*, carotid blood pressure (Hg.); signal equals respiratory movements; ¼ cc. curare injected intravenously leaving slight respiratory movements of mouth and flanks. Showing lung contractions following respiratory movements. *E* and *F:* Spontaneous contraction of lungs after a large dose of curare (½ cc. 1 per cent) completely paralyzing all striated muscles. *E*, lung isolated as in *A*. *F*, lung in normal attachment. Showing rhythmic lung contractions in the absence of external evidence of respiration. *G* and *H:* Water manometer records from inflated balloon in the stomach of the turtle; shell intact; stomach atonic and quiescent, but showing beginning of feeble rhythm at *c; a*, spontaneous respiratory movements, quick up and down stroke, followed by lung contractions; *b*, shown as diminished tension in the stomach because of the lowered intra-abdominal pressure created by the active lung contraction, the shell being intact. Time, 5 seconds.

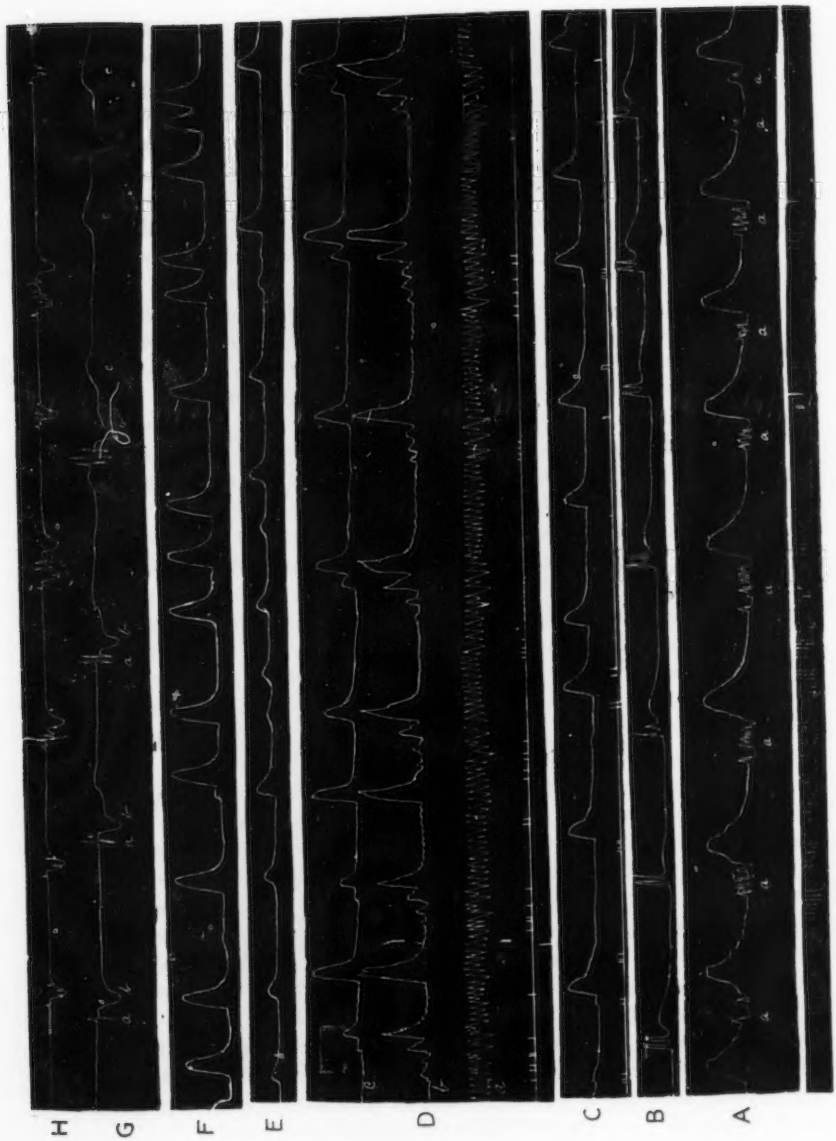

Fig. 3

figure 3, *A*, *B*, *C*. The lung contraction follows the respiration after a latent period of 1 to 3 seconds. In preparations in poor condition the latent period is usually much longer. If the external respiratory movements are of the Cheyne-Stokes type, the lung contraction does not appear until the end of the last respiration in the group, especially if the respirations come fairly close together, except in marked asphyxia. The lung contractions are usually absent when the external respiration is rapid and continuous. This absence appears to be due to inhibition of the center controlling the lung contractions by some process in the external respiratory act.

Under certain conditions acts of external respiration may be executed without being followed by a contraction of the lung. This is especially the case in animals in poor condition from any cause, in preparations in partial traumatic shock from the operative procedure, or if for any reason, such as apnea, the external respiration is feeble. By feeble we mean feeble discharges from the respiratory center. The general relation obtains that the stronger external respiratory act, the stronger the lung contractions that develop during the respiratory pause.

Graphic records of this strong lung rhythm may be obtained from an inflated balloon in the stomach of the turtle, provided the stomach is relatively quiescent and in low tonus (fig. 3, *G* and *H*). The external respiratory act induces passive changes in the intragastric pressure (fig. 3, *G*, *a*) just as in mammals, except reverse, that is, in the turtle expiration causes increased intragastric pressure and vice versa. The active lung contractions appear on the gastric balloon records as waves of negative pressure or lowered tonus, owing to the lung contraction increasing the general intra-abdominal negative pressure.

Tracings showing the lung rhythm as it appears after complete curarization are reproduced in figure 3, *E* and *F*. If a paralyzing dose of curare is injected intravenously in a preparation breathing spontaneously and regularly and exhibiting lung contractions as in figure 3, *A*, the brief central stimulation phase of the curare action, as shown by violent body movements and cardiac arhythmia, is followed by complete quiescence of the lungs lasting for one-half to two hours. This is not due to peripheral paralysis of the pulmonary motor nerve fibers. It is evidently due to paralysis of the medullary centers by curare. Reflex lung contractions can be secured before the spontaneous rhythm appears. But when the spontaneous lung rhythm reappears, it continues for hours or indefinitely provided suitable artificial respiration is carried out at intervals and a fairly efficient circulation maintained.

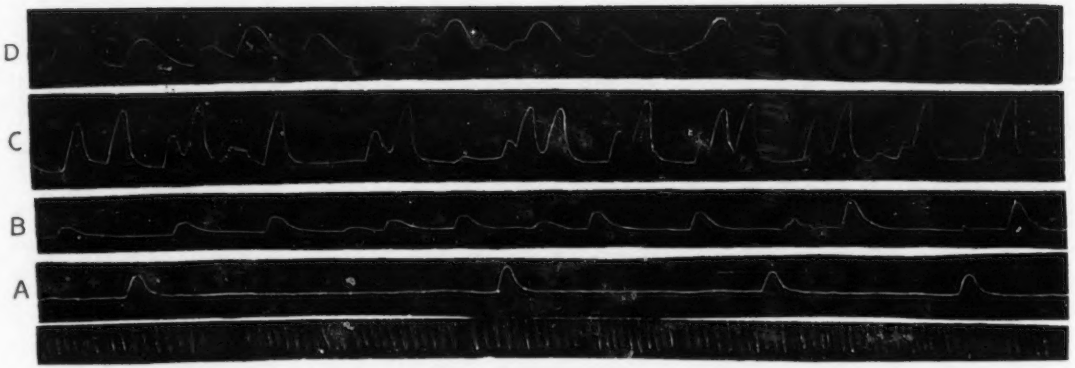

Fig. 4. Water manometer tracings of the rhythmical contraction of the turtle's lung after complete curare, abolishing skeletal and respiratory movements. Tracings *A* to *D* taken successively about 90 minutes apart. Time, 5 seconds. Showing the usual increased rate and amplitude of the lung contractions with increasing asphyxia of the brain.

The fact that the lung rhythm appears in completely curarized animals shows that it is not due to reflexes evoked by acts of external respiration. It shows further that central and efferent nervous processes of the external respiration go on during the curarized state, because these lung contractions are side events in the normal respiratory act.

These lung contractions following the external respiratory act have been studied and described by Francois-Franck (3), (4) in several species of reptilia. They are evidently identical with the active lung contractions following the respiratory act in frogs and salamanders, recently reported by us (13) and (14). It may be of some interest to note that in this regard the lung physiology of amphibia and reptilia is similar or identical, despite the fact that the mechanisms for effecting lung ventilation in these two groups of animals are entirely different.

2. As already noted, the lung contractions develop during the respiratory pause, and if the respirations come close together they may not appear at all, except in states of marked asphyxia. In fact, a lung contraction once begun may be weakened or cut short by an act of external respiration coming on before completion of the contraction. It would thus appear that while a single respiratory discharge from the respiratory center will, as a side effect, induce a lung contraction after a characteristic latent period, several respiratory discharges following in succession closer than this latent period of the lung contraction interferes with this development in such a way that the lung contraction follows the last respiratory act only. We have made very great efforts to determine the mechanism of this interference by satisfactory experiments.

On most of our tracings from the isolated lung, the animal breathing spontaneously by the lung on the intact side, there appears a tonus relaxation of the isolated lung during the period of external respiration, that is, prior to the active lung contraction. This may be seen in figure 3, *A*, and figure 6, *A*. If all purely mechanical factors were excluded, this would indicate a central inhibition of the lung tonus by discharges from the respiratory center prior to the central processes initiating the lung contractions. Francois-Franck (4), (5) has called attention to the fact that on stimulation of the peripheral end of the incompletely isolated vagus the lung contraction produced by this stimulation may be preceded by an apparent inhibition of the lung tonus, in reality due to mechanical factors developed in the body cavity as the

result of the contractions of some muscles of the neck. Furthermore, if the isolated and inflated lung presses against any structure in the body cavity with a force equal to or greater than the internal pressure maintained in the lung (1½ to 2 cm. water) and if these structures are so moved by the act of spontaneous inspiration that the pressure on the outside of the lung is decreased, the net result would be an apparent inhibition of the tonus of the isolated lung during the external respiratory acts. We endeavored to eliminate this source of error by complete curarization, by section of the spinal cord below the medulla, and by suspending the isolated lung partly outside the body cavity. In completely curarized preparations there is, of course, no external respiratory act, but the facts cited above go to show that the discharge from the respiratory center, after an initial paralysis, is resumed and continues rhythmically. Despite this fact inhibition of the lung tonus prior to the lung contractions rarely if ever appears on the tracings from our completely curarized animals. This may be due, however, to a depression of the medullary centers by the drug (direct chemical action, or indirect by altering or diminishing afferent skeletal nervous impulses) to such an extent that the tonus motor action of the medullary centers on the lung is abolished. Without such tonic motor action there could be no relaxation of lung tonus by central inhibition. This negative result on completely curarized animals is therefore no criterion of what the discharges from the respiratory center may do in the direction of central inhibition of lung tonus, when such central motor tonus is present.

We have secured tracings from animals partly curarized, from animals with section of the spinal cord in the neck, and from animals without curare or spinal cord transection, but with the observed lung suspended outside the body cavity, *indicating a central inhibition of the lung tonus by the discharge from the respiratory center, an inhibition prior to the motor innervation of the lung.* A tracing illustrating this fact is shown in figure 6, *B*. Water manometers are usually not delicate enough to disclose the inhibition. This inhibition is probably proportional to the amount of central motor tonus in the lungs.

From the point of view of utility or teleology this inhibition would be expected, as greater relaxation of the lung tonus means less resistance to lung inflation, and active lung contraction would counteract the inspiratory effort. The possible utility of the active lung contraction following the respiratory act is another matter. Useless, useful or harmful, it is there, and we are at present concerned only with the mechanisms of its initiation and control.

3. We desire to point out, however, that the above described relations of the external respiratory act to the active lung contractions are similar to the relation of the swallowing act to the peristalsis of the esophagus. If the swallowing acts are sufficiently far apart, each swallowing is followed by a peristaltic wave of the esophagus initiated from the medulla. If the swallowing acts are repeated at very brief intervals esophageal peristalsis follows the last swallowing act only. The parallel between swallowing-esophageal peristalsis and respiration-lung contraction appears complete, despite the very diverse functions of the two mechanisms. The lung has the same organogenesis as the esophagus, and the primitive mechanism for external respiration is swallowing, the active lung contractions following the respiratory act (air swallowing) serving probably a real respiratory function. As the mechanism of external respiration changes with the reptilia the organogenesis and primary nervous relations of the lung remaining the same, *the lung inhibition and contractions associated with the respiratory act may represent inherited mechanisms useless, if not at times actually harmful to animals provided with this later respiratory device. It may be a vestigial mechanism on the road to elimination in the process of evolution.*

4. The influence of asphyxia on the bulbar center for the lung rhythm appears to run parallel with the influence of asphyxia on the respiratory center. In curarized preparations permitted to go into varying degrees of asphyxia the lung rhythm increases in rate and intensity to the point of incomplete lung tetanus parallel with increasing asphyxia (fig. 4). It is clear that asphyxia increases the lung tonus by central motor action. The lung rhythm does not end in this state of incomplete tetanus. If the state of asphyxia is permitted to continue, the incomplete tetanus stage is followed by feebler lung contractions appearing at greater and greater intervals (5 to 10 minute intervals in some cases) before the final quiescence. This probably represents the well-known final feeble activity of the respiratory center when the asphyxia is carried beyond the point of stimulation to that of actual impairment of the center.

Further evidence of this complete parallel is furnished by the type of experiments illustrated in figure 5. Here artificial respiration through the intact lung, normal, *A*, and denervated, *B*, both preparations being completely curarized, inhibits the tonus and rhythm in non-asphyxiated preparations, *A*, evidently by inducing apnea, and diminishes the tonus and incomplete tetanus in the asphyxiated preparation, evidently by decreasing the asphyxial condition of the blood.

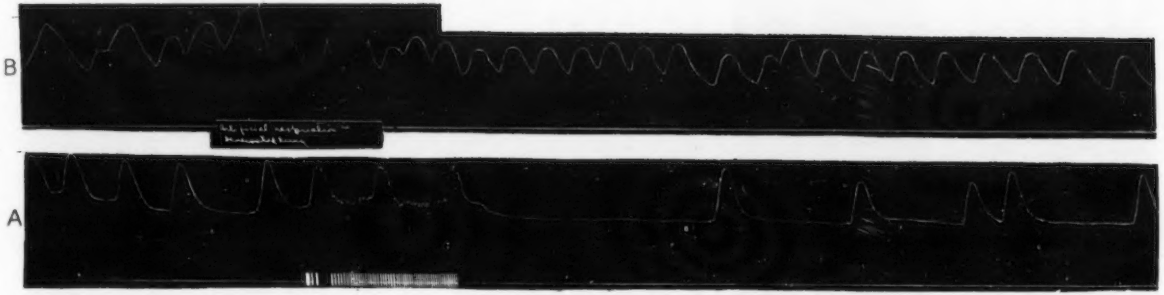

Fig. 5. Water manometer tracings of the intrapulmonic pressure in the turtle. Animals decerebrated and completely curarized; record from left lung isolated except pulmonary vagi branches and lung blood vessels. Cannula in tip of lung. *A:* right lung intact; signal, artificial respiration in right lung, showing inhibition of lung rhythm of the isolated lung. *B:* right lung intact but isolated from central nervous system by section of right vagus in neck. Signal, artificial respiration in right lung. Showing inhibition of the incomplete tetanus of the left isolated lung, through aeration of the blood.

In non-curarized preparations, in which one can follow the action of the respiratory center by means of the external respiratory acts, contractions of the isolated lung, not related to any external respiration, may appear during asphyxia. It appears that asphyxia may occasionally disorganize the normal correlation between the respiratory center and the vagi center controlling the lung contractions, and that asphyxial conditions are capable of stimulating the latter centers directly.

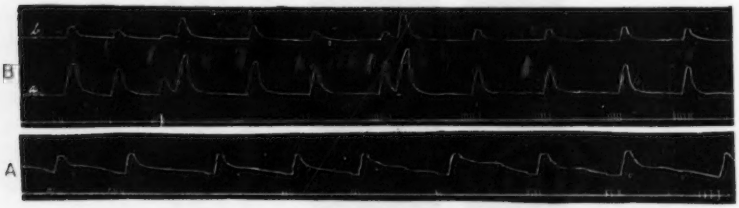

Fig. 6. Tracings of the intrapulmonic pressure in the turtle. Left lung, isolated except pulmonary nerves and blood vessels. Left bronchus ligated. Cannula in tip of lung. Animals decerebrated. Right lung left in normal relations. *A:* signal, spontaneous respiration. Showing inhibition of tonus of isolated lung during respiratory movements followed by strong contraction of lungs. Water manometer. *B:* animal partially curarized, having respiratory muscles in feeble activity. Signal, spontaneous respiratory movements. Both tracings from left isolated lung. *a*, record from delicate tambour; *b*, water manometer. Showing lung contractions following spontaneous respiratory movements, preceded by tonus inhibition, as revealed by tambour, the water manometer not being delicate enough to register the tonus inhibition.

THE RÔLE OF THE EFFERENT PULMONARY VAGI FIBERS AND THE VARIOUS PARTS OF THE BRAIN IN THE GENESIS OF THE RHYTHMIC LUNG CONTRACTIONS

1. In the species of turtle studied by us the spontaneous lung contractions are of central origin, and the motor innervation is through the vagi, as shown by Kahn (8) and François-Franck (5) for the common land turtle of Europe. This may be shown by experiments such as reproduced in figure 7, *A*. In that case the animal was completely curarized, graphic records being taken of the lung contractions both from the isolated and the intact lungs. The intact lung has, of course, its sympathetic nerve connection intact. Nevertheless section of the vagus nerve on the side of the intact lung abolishes the strong contractions in that lung at once and forever. The section of one vagus

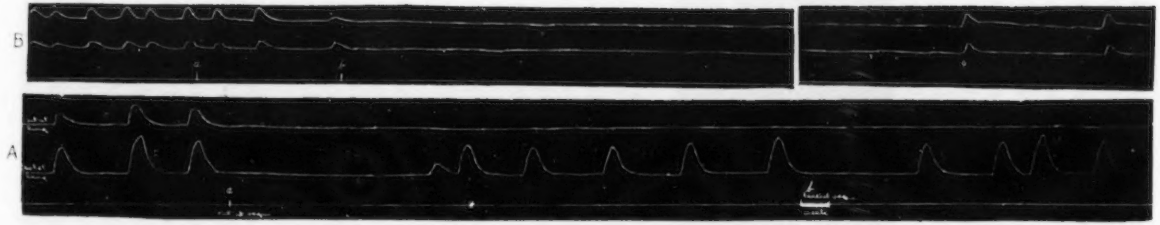

Fig. 7. Water manometer tracings of the intrapulmonic pressure in the turtle. *A* and *B:* upper tracing in each case, right or intact lung; lower, left or isolated lung. Animal completely curarized, after previous decerebration. *A: a,* section of right vagus in neck showing complete abolition of rhythmic lung contractions in right lung and temporary inhibition (reflex) of contraction of left lung. *b,* stimulation of central end of right vagus with weak tetanizing current, showing reflex inhibition of the left lung, that is, inhibition of the medullary center. *B: a,* beginning isolation of spinal cord in the neck. *b,* section of spinal cord in neck, showing reflex inhibition ("shock") of the medullary center governing the rhythmic lung contractions.

stops the contraction of the lung on the opposite side temporarily through stimulation of afferent inhibitory fibers in the vagus trunk depressing the medullary centers. It is thus clear that the motor innervation of the lung rhythm is solely through vagi nerves. The same fact can be illustrated by the use of atropine. Atropine paralyzes the vagi motor fibers in the lungs. The tracing reproduced in figure 8, *C*, was secured from the left lung of a completely curarized preparation, the lung being isolated from the body except for the pulmonary blood

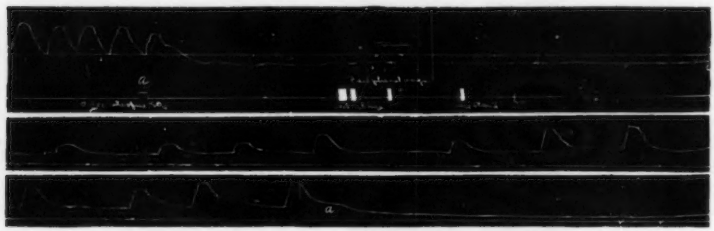

Fig. 8. Water manometer tracings of the intrapulmonic pressure in the turtle. Animals decerebrated. Left lung isolated, cannula in tip; right lung in normal relations. *A* and *B*, showing lung contractions following the spontaneous respiratory movements. *A: a*, section of right vagus in neck, followed by temporary inhibition (central) of the tonus and contractions of the opposite lung, also temporary inhibition of the respiratory movements. The latter reappear at *X*, but are not followed by lung contractions. Tracing *B* is continuation of *A* after a 6 minute interval, the lung contractions gradually regaining normal vigor. *C:* animal completely curarized; lung in strong tonus and contractions, probably from partial asphyxia. *a*, intravenous injection of ½ mgm. atropine sulphate followed by permanent inhibition (peripheral action) of lung tonus and contractions. Signal shows vagus stimulation is without effect on lung.

These tracings indicate a tonic condition of the medullary center controlling the lung motor tissues. This center is more profoundly influenced by depressant impulses ("shock"?) than is the respiratory center.

vessels and pulmonary vagus branches. Intravenous injection of 0.5 mgm. atropine sulphate abolished the lung rhythm promptly just as it abolished the motor action of the vagus on the lung musculature.

The reader's attention may again be directed to the fall in lung tonus induced by peripheral vagus paralysis of atropine and by afferent depressor impulses acting on the medulla (fig. 8, *A* and *C*). The tracings in figure 8 show at least that under some conditions (partial asphyxia) the medulla-vagi-lung motor mechanism is in a state of tonic activity, in which the stronger rhythmic contractions are superimposed much

like the constant tonus and the occasional peristaltic contractions of the gut. We have so far been unable to demonstrate this tonic activity under more nearly normal conditions; but our results point in the direction of some normal motor tonus.

2. The inhibition of the contractions of the lung on the opposite side induced by section of one vagus (afferent inhibition of a central automatism) is usually more prolonged than shown in figure 7, *A*. In preparations not curarized it can be shown that section of one vagus temporarily inhibits both external respiration and the tonus and contractions of the lung on the opposite side, the external respiratory acts returning sooner than the lung contractions.

Section of the spinal cord in the neck also produces a very prolonged inhibition of the medullary center initiating the lung rhythm (fig. 7, *B*). This central inhibition or shock is shown not only by the temporary abolition of the spontaneous rhythm, but also by the lowering of the excitability of these centers to reflex stimulation leading to lung contractions.

3. As reported by many previous investigators, stimulation of the peripheral end of the vagus nerve in the turtle causes contraction of the lung musculature (fig. 9, *C*). We have never seen any inhibitory effects on the lung in the turtle from stimulation of the peripheral vagus. This appears to us significant in view of the fact that in the frog the predominant action of the vagi on the lungs is inhibitory, and in the most primitive amphibian lung (necturus) all the efferent lung nerve fibers appear to be inhibitory.

In the species of turtle studied by us the motor action of the vagi on the lungs is strictly unilateral. Single induction shocks (make or break) applied to the peripheral vagus will not cause lung contractions unless exceedingly strong. Weak tetanizing currents applied to the vagi induce an incomplete tetanus or rhythm that seems to indicate a certain degree of refractory state in the peripheral mechanism. Strong tetanization of the vagi will, however, induce curves of complete tetanus closely resembling those of an ordinary muscle nerve preparation (fig. 9, *C*).

In view of the identity of origin and certain similarities in the nervous control of the lung and the alimentary canal, we made some comparisons between the vagi motor action on the lungs and on the stomach (fig. 10). The latent period of the vagi motor action on the stomach is very much longer than its motor action on the lung. The turtle's stomach cannot be tetanized by vagus stimulation; the lungs can be

tetanized. The third marked difference is the quick failure of vagus motor action on the stomach on repeated stimulation in comparison with the repeated tetany of the lungs that may be induced by vagus stimulation. These differences may be due, in part, to the fact that in the turtle the vagi carry inhibitory efferents to the stomach in addition to the motor, while the efferent vagus lung action is solely motor. The differences also suggest that the gut has retained more of its primitive automatism (independent peripheral nervous system) while the

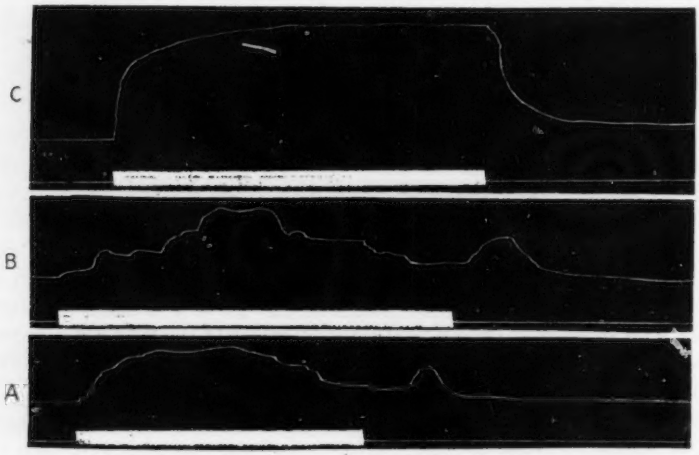

Fig. 9. Water manometer tracings of the contractions of the isolated lung of the turtle. Animal decerebrated and completely curarized; left lung isolated except for pulmonary vagi fibers and blood vessels. Cannula in left bronchus. Stimulation with moderately strong tetanizing current, *A*, optic lobes, *B*, medulla, *C*, peripheral end of left vagus, showing incomplete and complete tetanus of the lung musculature.

differentiation in the lung has been toward the more simple relations of a muscle nerve preparation.

4. In 1878 Martin reported that stimulation of the optic lobes in the frog accelerates the external respiratory movements. Since that time several investigators have concerned themselves with the problem of accessory respiratory centers above the level of the medulla. Recently Coombs (12) reported that stimulation of the optic lobes or the medulla in the turtle with weak tetanizing current causes lung contractions via the vagi nerves.

As we have shown, the normal rhythmic contractions of the turtle lung are side events in the external respiratory act. This being the case, we would expect lung contractions from stimulation of any part

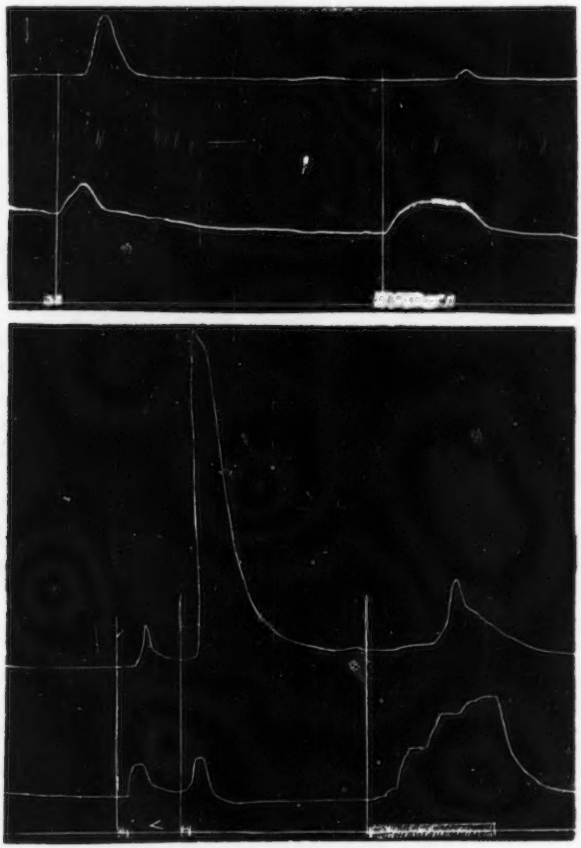

Fig. 10. Simultaneous water manometer tracings of the stomach and the lung contractions on stimulation of the peripheral end of the vagi nerves in the turtle. In *A* and *B*, upper record from stomach (balloon method); lower record from left lung, isolated except for the pulmonary blood vessels and vagi fibers; cannula in left bronchus. Signal, stimulation of peripheral end of left vagus with the tetanizing current. Showing longer latent period, more rapid fatigue and absence of tetanus in the gastric response to vagus stimulation.

of the central nervous system that has motor connections with the medullary respiratory center. This has turned out to be a fact, at least as regards the optic lobes. In figure 9, *A* and *B*, are reproduced typical tracings of the incomplete tetanus the lung induced by stimulation of the optic lobes and the medulla with weak tetanizing currents. The lung contraction curves induced from the optic lobes and from the medulla in completely curarized turtles are practically indistinguishable. Both centers fail quickly under this type of stimulation and there is a single after-discharge (lung contraction) that appears more normal than the contractions induced directly by the stimulation. Complete tetanus of the lungs cannot be induced by central stimulation, evidently because of central refractory states.

A tonus rhythm or spontaneous contraction of the lung after section of the vagi nerves similar to that described by Fano and Fasola (2) in the European turtle, has been seen occasionally in our turtle preparation, when we used an exceedingly delicate tambour as a recording device. The contractions are feeble but slow and regular. They may persist for hours (fig. 23, *A*). It is probable that a peripheral automatic motor mechanism of the lung is present in all species of turtle, although it may differ in degrees in various species; but it requires not only delicate recording devices but, above all, animals in prime condition to reveal it. It is certain that parallel with the development of the new type of external respiratory mechanism in the reptilia, the peripheral lung motor automatism, so prominent in the amphibia, has retrograded or has been changed to one of primarily medullary origin.

LUNG REFLEXES

1. Lung reflexes from sensory stimulation of the respiratory tract: a. The pulmonary branches of the vagi contain two kinds of afferent fibers acting on the medullary center, one type causing reflex lung contraction in a quiescent preparation, or acceleration of the contractions in an active preparation. The other type causing inhibition of the tonus in the case of quiescent preparations or of the contractions in active preparations. For the sake of brevity we call these motor and inhibitory afferents, respectively. The motor afferents are stimulated by inflation as well as by deflation of the lung (fig. 11) or by the weak tetanizing current. Strong tetanizing currents, on the other hand, stimulate the inhibitory afferents. In all these experiments the lung inflation and deflation, and the direct stimulation of the central and of the pulmonary

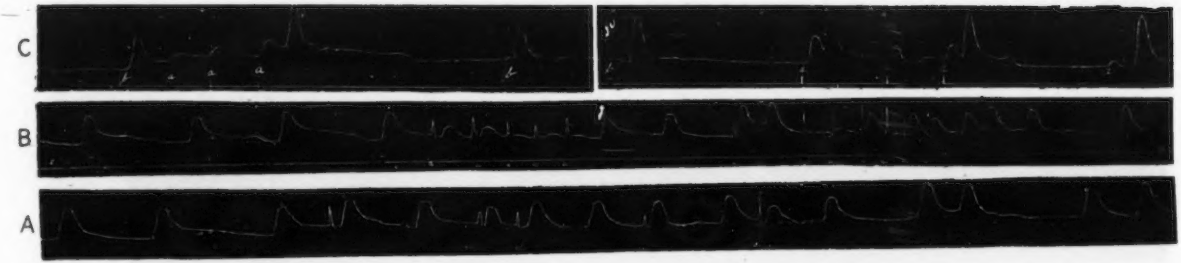

Fig. 11. Water manometer tracings of the intrapulmonic pressure in the turtle. All records from the left isolated lung; cannula in tip of lung. Animals decerebrated. Right lung intact. *A:* Animal completely curarized and showing contractions of isolated lung. *a*, single inflations (positive air pressure) in the intact lung, showing reflex contractions of opposite lung. *B:* animal not curarized. Signal, spontaneous respiration; *a*, single inflation of right or intact lung, showing reflex contractions and also evidence of central refractory state. *C:* Animal completely curarized, spontaneous lung rhythm absent; *b*, single inflation (positive pressure); *a*, single deflation of right or intact lung, showing reflex contraction into opposite lung both from deflation and inflation.

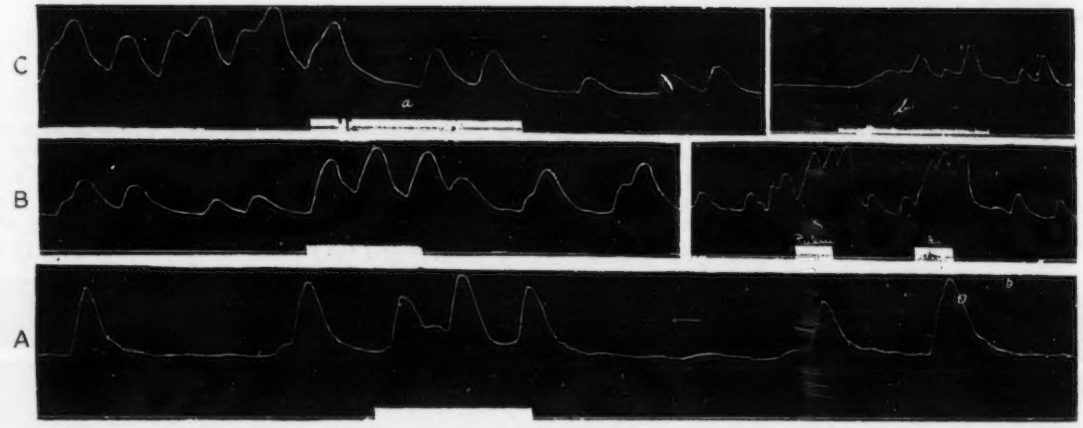

Fig. 12. Water manometer tracings of the intrapulmonic pressure in the turtle Animals decerebrated and completely curarized. Records from left lung, isolated, except for pulmonary blood vessels and nerves. Cannula in tip of lung; bronchus ligated. *A* and *B:* stimulation of central end of pulmonary branches of right vagus with weak tetanizing current, showing reflex augmentation of the spontaneous lung rhythm. *C:* stimulation of central end of pulmonary vagi (right) with strong tetanizing current, showing inhibition of the spontaneous lung rhythm, *a*, and initiation of this rhythm in the quiescent preparations *b*.

vagi, we used, of course the lung and vagus on the opposite side to the lung serving to record the contractions. In no case did we note the inhibitory afferents being stimulated by lung inflation or lung deflation.

Typical tracings showing the reflex lung contraction on lung inflation and deflation are given in figure 11. Tracings showing the opposite reflex effects on weak and on strong tetanization of the central end of the pulmonary vagi are reproduced in figure 12. The pulmonary motor afferents can also be stimulated by other mechanical means, for example, rubbing the collapsed lung of one side between one's fingers induces reflex contraction in the opposite side via the medulla.

Reflex lung tetanus cannot be produced by lung deflation or inflation, that is, the active change in the intrapulmonic pressure, and not the state of continued inflation or collapse that acts as stimulus to the motor afferents.

In preparations not curarized, but breathing normally by means of the intact lung, single inflation of the intact lung during a respiratory pause usually gives a reflex lung contraction; but if the inflation is made shortly after completion of a spontaneous contraction by the isolated lung, the reflex may not be elicited. The same is true if a series of lung inflations is produced with very short intervals between each inflation. These facts evidently point to a condition of refractory state of the medullary reflex center, unless the phenomenon can be due to simultaneous stimulation of the inhibitory pulmonary afferents.

In turtle preparations in good condition deflation of one lung by suction through the trachea invariably initiates or accelerates the external respiratory movements. Lung inflation, on the other hand, may start a respiratory movement or it may temporarily inhibit the external respiration. It is thus evident that stimulation of the pulmonary motor afferents by lung inflation may initiate reflex lung contractions by acting on the medullary motor center directly, the discharge of the respiratory center not being a necessary link in the chain.

We have found that a single inflation of the intact or isolated lung aerates the blood, accelerates the heart and by so doing improves the circulation through the medullary centers because of the increase in the general arterial pressure. It is certain however that the contraction of the isolated lung following one or more inflations of the intact lung does not occur because of the improved circulation of a more highly oxygenated blood through the medullary lung center; for this reflex contraction persists not only following the inflation of a lung the

pulmonary vessels of which have been occluded by a temporary ligature but can be elicited for a considerable time after the complete excision of the heart. On the other hand, it is not obtained from the isolated lung following a single or several inflations of the denervated but otherwise intact lung of the opposite side.

We designate the reflex inhibition of lung tonus and contraction by strong tetanization as due to a separate type of sensory fibers, the inhibitory afferents, at the same time keeping in mind the possibility that this inhibition may in reality be due to abnormally strong or

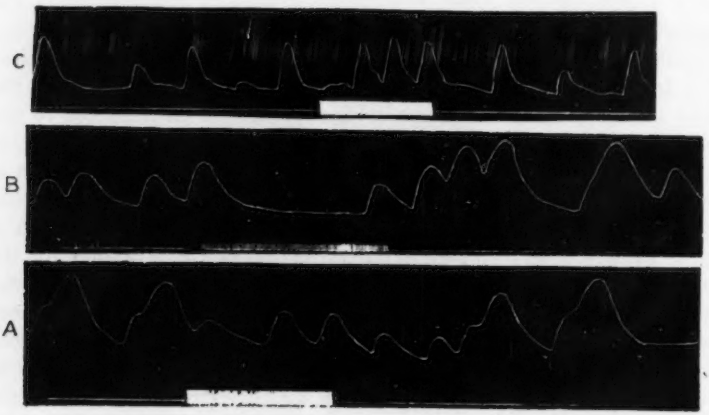

Fig. 13. Water manometer tracings of the intrapulmonic pressure in the turtle. Animals decerebrated and completely curarized. Records from left lung isolated except from pulmonary blood vessels and vagi branches. Cannula in left bronchus. *A* and *B:* stimulation of central end of recurrent laryngeal nerve, showing reflex inhibition of the lung rhythm. *C:* stimulation of central end of gastric branches of right vagus, showing reflex augmentation of the lung rhythm.

abnormally rapid series of impulses over the motor afferents impinging on the central automatic mechanism. This stimulation also inhibits the external respiratory movements.

b. Stimulation of the central end of the inferior or recurrent laryngeal nerves causes invariably reflex inhibition of the lung tonus and contractions (fig. 13, *A* and *B*). At no time was reflex lung contraction obtained from the central end of this nerve. Motor afferents for the lung reflex are either absent or the inhibitory afferents are so predominant that the action of the former type is entirely suppressed on simultaneous stimulation of the two types.

Observations on the effects of external respiration of stimulation of the central end of the inferior laryngeal were not made but in connection with this reflex depression of the lung contraction mechanism we can state that mechanical tension or pulling on the trachea causes profound depression of the respiratory center (fig. 14). Mechanical stimulation of the larynx and glottis (rubbing with blunt probe) on the other hand induces strong lung contractions.

c. Mechanical stimulation (gentle rubbing) of the posterior nares causes very powerful lung contractions. If the stimulation is long-

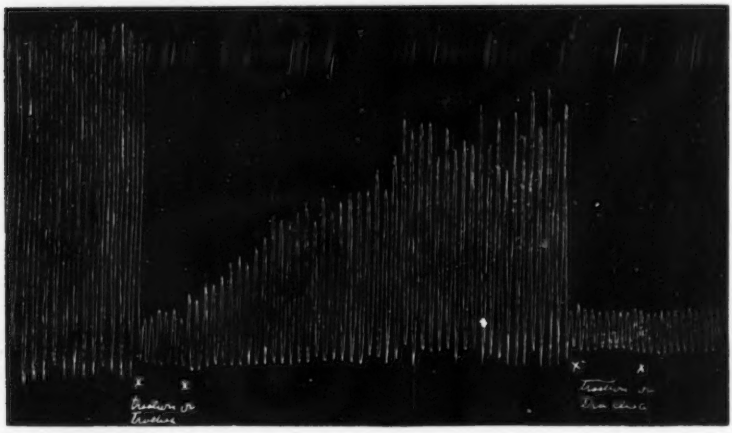

Fig. 14. Tracing of respiratory movements (water manometer) in the turtle. Animal decerebrated; cannula in trachea, rapid respiration due to partial asphyxia; x–x', strong forward traction on trachea, inducing a temporary depression of the respiratory center, probably through stimulation of the recurrent laryngeal nerves.

continued the lung goes into incomplete tetanus. This stimulation initiates lung contractions in quiescent preparations and accelerates the rhythm in active preparations. When the nares are thus stimulated in decerebrated but non-curarized preparations such stimulation induces most violent respiratory efforts and general struggling.

In general the reflex lung contractions evoked from the nares are more powerful than those produced by stimulation of any other region of the respiratory tract. It is one of the last lung reflexes to disappear as the preparation deteriorates from circulatory failure, and other

causes, in long continued experiments. Reflex lung contractions from the nares can be obtained in preparations with the medullary center in such poor condition ("reflex shock") that the spontaneous external respiratory act is not accompanied by lung contraction, all of which point to the fact that the sensory nerve fibers of the posterior nares make strong motor connection with the medullary center controlling the lung contraction. Stimulation of the posterior nares with chemical irritants were not tried.

2. Lung reflexes from spinal sensory nerves: Weak tetanizing of the central end of any spinal nerve causes reflex lung contraction. Most of the tests were made with the sciatic and the large brachial nerves. Weak stimulation accelerates the rhythm in an active preparation and

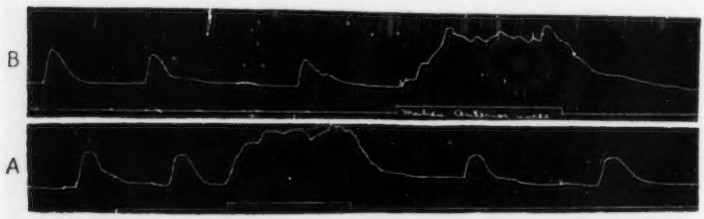

Fig. 15. Water manometer tracings of the intrapulmonic pressure in the turtle. Records from isolated left lung, cannula in left bronchus, pulmonary vagi fibers and blood vessels being intact. Animal decerebrated. *A*, animal completely curarized; *B*, animal not curarized. Signal, mechanical stimulation of the nares, showing incomplete tetanus (reflex), of greater amplitude than that of the rhythmical lung contractions.

initiates a rhythm in quiescent preparations (fig. 16, *A*, fig. 17, *A*). Strong stimulation induces incomplete lung tetanus (fig. 16, *B* at x-x', fig. 17, *C*). In quiescent preparations the incomplete lung tetanus may be followed by brief periods of apparently spontaneous lung rhythm (fig. 17, *B*).

If the preparations are in good condition gentle rubbing of the skin causes lung contractions. Pinching, crushing or cutting the skin causes powerful motor reflexes into the lung (fig. 16, *C*), even when the reflex excitability is not at its maximum. Strong lung contractions are likewise induced by mechanical (rubbing with a blunt probe) or electrical stimulation of the cornea.

Reflex inhibition of the lung tonus or the rhythmical contractions were not obtained from the spinal sensory nerves by any mode of stimulation.

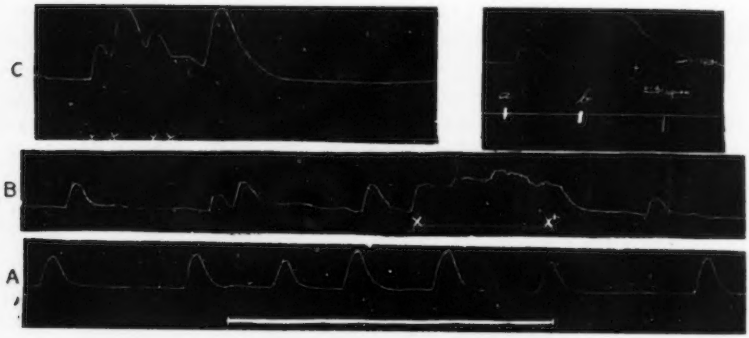

Fig. 16. Water manometer tracings of the intrapulmonic pressure in the turtle. Animals decerebrated and completely curarized. Records from left lung, isolated except for pulmonary blood vessels and vagi nerves. Cannula in tip of lung, bronchus ligated; *A:* light stimulation; *B:* stronger stimulation of central end of sciatic nerve, showing acceleration and incomplete tetanus of lung rhythm. *C: a,* stroking of skin of hind leg with finger; *b,* pinching toes of hind leg, *x,* cutting skin of hind leg. Showing reflex lung contraction on stimulation of cutaneous nerves.

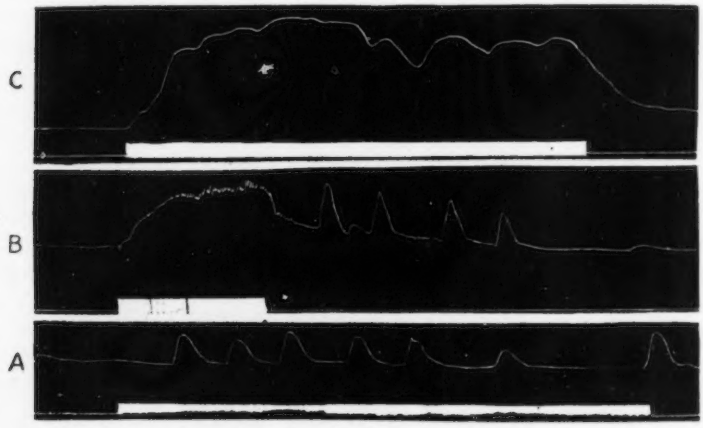

Fig. 17. Water manometer tracings of the intrapulmonic pressure in the turtle. Animals decerebrated and completely curarized. Records from left lung, isolated, except for pulmonary blood vessels and nerves. Left bronchus ligated; cannula in tip of lung. Preparations showing no spontaneous medulla-lung rhythm. Signal, stimulation of central end of sciatic nerve with tetanizing current. Showing reflex development of lung rhythm and lung tetanus.

3. Lung reflexes from the visceral sensory nerves: a. The alimentary tract. Reflex lung contractions may be obtained from practically every part of the alimentary canal, the most powerful being the lung contractions following stimulation of the lower end of the gut (cloaca, rectum, large intestine). Mechanical distention with balloon, rubbing, pressure, cutting or crushing this end of the alimentary canal causes contractions in the lung. (fig. 18, *B, C, Da, Dd*; fig. 19, *a, c*). In fact, one may induce incomplete tetanus of the lungs by strong stimulation of the lower end of the gut.

Mechanical or electrical stimulation of the small intestines also induces lung contractions (fig. 19, *b, d*). Similar lung reflexes are induced by stimulation of the central end of the gastric vagi branches (fig. 13, *C*), and by direct stimulation of the esophagus. But the contractions of the empty stomach, even when most vigorous, do not influence the lung motor mechanism.

Inhibition of the lung tonus and contractions were not seen as a result of artificial stimulation of the gut. But it seems clear that the afferent nerves of the alimentary canal, especially the oral and anal ends, make motor connections with the lung medullary centers.

b. The genito-urinary tract. Powerful lung contractions are induced by mechanical distention, pinching, crushing, tearing or electrical stimulation of the urinary bladder (fig. 18, *A*; fig. 19, *c, b*). Electrical or mechanical stimulation of the ureters, penis, prepuce and testis also produces motor reflexes into the lungs (fig. 18, *Dc*; fig. 19, *f, j*). As in the case of the alimentary tract, no reflex inhibitions into the lung were secured from the genito-urinary tract. In several female specimens the ovaries and the oviducts were stimulated, without any reflex influence on the lungs. Stimulation of the kidneys also yielded nothing definite in the way of lung reflexes. The most powerful and consistent lung reflexes in this group are those elicited from the urinary bladder.

c. The visceral sympathetic nerves. Outside the alimentary, the genito-urinary and the respiratory tracts no systematic or long-continued work was made on possible lung reflexes from the viscera, except for the stimulation of the central ends of the main visceral sympathetic nerves and connections. We may note, however, that the stimulation of the central end of the cardiac vagi branches has no effects on the lung. Reflex lung contractions were, on the other hand, obtained from the gall bladder, liver (fig. 19, *g*), and from the spleen.

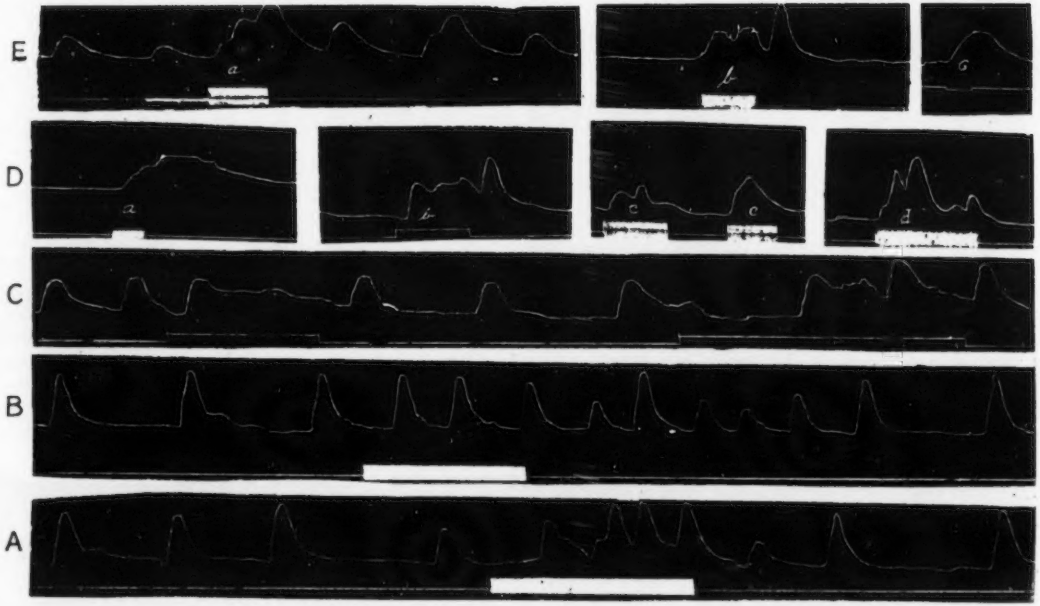

Fig. 18. Water manometer tracings of the intrapulmonic pressure in the turtle. Animals decerebrated and completely curarized. Records from left lung, isolated except for pulmonary blood vessels and vagi branches. Cannula in left bronchus. *A:* signal, distention of urinary bladder with balloon. *B:* signal, distention of rectum and large intestine by balloon, showing reflex augmentation of the lung rhythm. *C:* signal, mechanical stimulation of cloaca, showing reflex increase of lung rhythm. *D:* preparations showing no spontaneous lung rhythm; *a*, mechanical stimulation of cloaca; *b*, mechanical stimulation (pinching) of urinary bladder; *c*, mechanical stimulation (pinching) of penis; *d*, mechanical stimulation (pressing between fingers) of large intestine, showing reflex lung contractions. *E: a* and *b*, mechanical; *c*, electrical, stimulation of cornea, showing reflex lung contractions.

Fig. 19. Water manometer tracing of the intrapulmonic pressure in the turtle. Animal decerebrated and completely curarized. Tracing from left lung, isolated except for the pulmonary branches of the vagus and the blood vessels. Cannula in left bronchus. Preparation showing no spontaneous lung rhythm. *a*, Stimulation of rectum with strong tetanizing current; *b*, stimulation of small intestine, with strong tetanizing current; *c*, stimulation of urinary bladder, with strong tetanizing current; *d*, rubbing small intestine between fingers; *e*, cutting large intestine; *f*, pressing testes between fingers; *g*, rubbing urinary bladder between fingers; *h*, tearing wall of urinary bladder; *i*, rubbing tip of right lung between fingers; *j*, strong electrical stimulation of the right ureter. Showing reflex lung contractions and lung tetanus from stimulation of visceral sensory nerves.

The stimulation (electrical) of the central end of the visceral sympathetic nerves was made in a great many preparations, some in good, some in poor reflex conditions. The results are positive, that is, the stimulation of the visceral sympathetic nerves gives reflex lung contractions (fig. 20). The reflex lung contractions are particularly powerful from nerves *2*, *3* and *4* (fig. 2), these probably representing the group of splanchnic sympathetic nerves of the higher animals.

Reflex inhibitions of lung tonus and of lung contractions were never seen as results of stimulation of the central end of the visceral sympathetics.

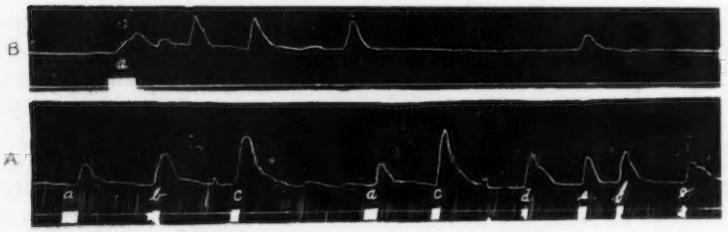

Fig. 20. Water manometer tracings of the intrapulmonic pressure in the turtle, showing reflex lung contractions on stimulation of the central end of various sympathetic nerves. Animals decerebrated and completely curarized. Record from isolated left lung; cannula in left bronchus. Preparations showing no spontaneous lung rhythm. *A:* stimulation with tetanizing current; *a*, nerve 2 (see fig. 2); *b*, nerve 3; *c*, nerves 2 and 3; *d*, nerve 4; *e*, nerve 5; *f*, nerve 6; *g*, nerve 7. *B: a*, stimulation with tetanizing current of nerves 2 and 3, showing reflex initiation of a temporary lung rhythm.

Results at times positive at times negative were obtained from the central end of the cervical sympathetic (fig. 2). In some preparations the stimulation of this nerve induced what appeared to be a reflex lung contraction, in other preparations, in equally good reflex condition, the stimulation had no effect on the lung. It appears, therefore, that afferent components in the cervical sympathetic nerve trunk are few in number and variable in their central action, at least as regards their influence on the medullary centers controlling lung tonus and lung contractions.

As the preparations are deteriorating the lung reflexes evoked from the visceral sympathetic nerves usually fail sooner than those called forth by stimulation of the spinal sensory or the afferent nerves of the respiratory tract itself. The cloaca, rectum and urinary bladder are

an exception to this rule, the lung reflexes evoked from these organs usually persisting to the end of all reflex response of the animal.

4. The influence of visceral sensory nerves on the respiratory center. We have shown that, excepting the inferior laryngeal (inhibition), the cardiac vagi (no action), the cervical sympathetic (inconstant), and strong stimulation of the pulmonary afferents (inhibition), sensory stimulation, spinal and visceral, induces reflex lung contractions. Since lung contraction is a normal adjunct to the external respiratory act it is pertinent to ask whether these lung reflexes are not secondary to the initiation or acceleration of discharges from the respiratory center. What effects have these sensory stimuli on the rate and intensity of the external respiratory movements? The turtle appears to be no exception to the rule that stimulation of spinal sensory nerves accelerates or initiates external respiration. As regards the spinal sensory nerves, therefore, we have a complete parallel between effects on external respiration and on lung contractions. Both are positive.

In regard to the visceral sensory stimulation the results are not so clear. In the first place much of our reflex work was done on completely curarized animals, preventing parallel observation on the external respiration. We can state, however, that so far as our observations go, stimulation of the abdominal sympathetic nerves induces reflex contraction of the respiratory muscles as an invariable result. But discrepancies appear when we come to the stimulation of some of the visceral organs, especially the cloaca, rectum and urinary bladder. As already pointed out the mechanical or electrical stimulation of these organs causes reflex lung contractions and never any inhibition, at least in curarized preparations. But the same type of stimulation of these organs in non-curarized preparations may cause pure inhibition of the external respiration, as witness the tracing reproduced in figure 21. We are dealing here with two possibilities, viz., *a*, stimulation of some of the visceral sensory nerves induces opposite effects on the two medullary centers depressing the respiratory center and stimulating the lung motor center; or *b*, the visceral afferents may have both effects on the two centers, the end result (depression or stimulation) depending on the intensity and rate of the artificial stimulation, the central action of curare tending to reveal only the stimulation action on the lung motor mechanism. Further work is required to establish either or both of these possibilities.

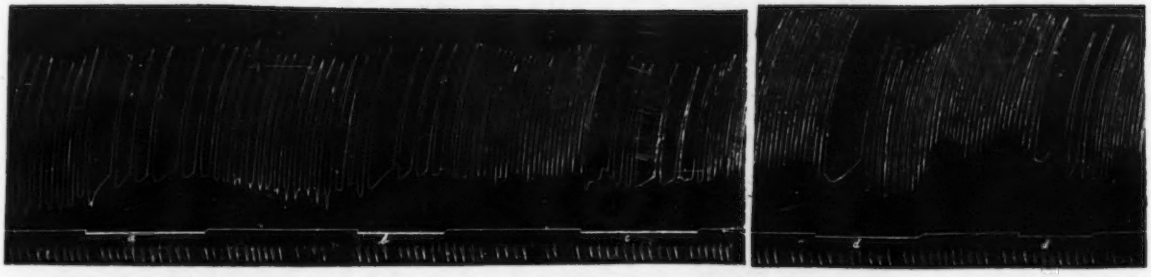

Fig. 21. Water manometer record of respiratory movements in the turtle; animal decerebrated; dorsal shell removed on left side; left lung isolated and left bronchus ligated. Right lung intact; cannula in trachea. *a*, Distention of rectum and lower part of large intestine by inflation of small balloon; *b*, electrical stimulation of the rectum; *c*, distention of urinary bladder by inflation of small balloon; *d*, electrical stimulation of urinary bladder, showing reflex inhibition of respiratory movements by stimulation of afferent nerves in large intestine, rectum and urinary bladder.

RESULTS ON THE SNAKE

1. Spontaneous lung contractions. If the external respiratory acts are not too close together, each act of external respiration is followed by a contraction of the lung. These lung contractions are feeble and of very short duration (fig. 22, *A*). If the attempts at external respiration come close together lung contractions appear only occasionally or rather during the respiratory pauses (fig. 27, *Ca*).

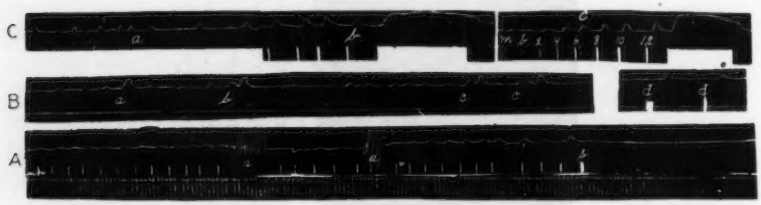

Fig. 22. Tracings (delicate air tambour) of the intrapulmonic pressure in the snake. Spinal cord cut and pithed below the medulla. Lung isolated; cannula in tip, trachea ligated. *A:* signal, spontaneous respiratory movements, showing lung contractions following each attempt at respiration; *a*, artificial respiration through cannula in tip of lung; *b*, pithing of brain followed by cessation of lung contractions. *B: a*, mechanical stimulation of skin of the head; *b*, mechanical stimulation of the cornea; *c*, mechanical stimulation of nares; *d*, electrical stimulation of central end of left vagus—showing reflex lung contractions. *C: a*, lung contractions following spontaneous respiratory efforts; *b*, tetanizing of both peripheral vagi; *c*, stimulation of the peripheral vagi with increasing number of electrical shocks—showing that motor discharge to lungs following respiratory movements is nearly maximal, as brief tetanizing of vagi produces only slightly greater lung contractions and that the vagi-lung muscle reacts to electrical stimulation like an ordinary nerve-muscle preparation. Time, 5 seconds.

These lung contractions in the snake appear to us too feeble to be of any value in the respiratory exchange of the lung.

2. Lung reflexes. Reflex lung contractions can be induced by the stimulation of the central end of one vagus, the other vagus being intact, and by stimulation of the nares, the cornea and the skin of the head region (fig. 22, *B*). The lung contraction following stimulation of the central end of one vagus is invariably preceded by an act of respiration, that is, a discharge from the respiratory center. The other reflex lung contractions may appear without being preceded by attempts at external respiration.

3. Rôle of the pulmonary vagi. Section of both vagi abolishes the lung contractions associated with the acts of external respiration. Stimulation of the peripheral end of either vagus causes contractions of the lung. These lung contractions appear to be confined to the upper third of the lung, that is, to the alveolated part or lung proper. It is a singular fact that, with one exception, all the paired lung reptilia thus far investigated, the lung motor action of the vagi is strictly unilateral, while in this species of snake both vagi act on the one lung. And it appears that the one-lunged condition of most snakes is due not to fusion of the original pair but to atrophy of one of the pair.

The lung motor fibers in the vagi of this snake can be stimulated with single induction shocks more readily than in the turtle. There is also less evidence of a tendency to an all-or-none motor response in the snake lung. In fact so far as our experiments go the vagus lung musculature behaves much like an ordinary nerve preparation.

Lung inhibitions from stimulation of the peripheral vagi were never observed. Destruction of the brain or section of both vagi neither decreased or increased the peripheral lung tonus. The lung vagi motor mechanism is either not in tonic activity or our method of preparing the animal abolishes this tonic activity through central "shock."

While our work on the snake was limited to eleven rather small specimens, the results indicate the essential parallel of the lung motor physiology in the snake and the turtle, namely, the vagi motor control and lung reflexes from the head origin of the animals. We have never observed a peripheral lung motor mechanism in the snake after section of the vagi.

THE DIRECT INFLUENCE OF THE SYMPATHETICS ON THE LUNG MOTOR TISSUES

Jackson and Pelz (7) have published tracings apparently showing strong inhibition of the lung tonus on stimulation of the central end of the cervical sympathetic nerve. These investigators also state that strong stimulation of this nerve may induce lung contractions of greater amplitude than that caused by stimulation of the peripheral end of the vagus. We have made great efforts to verify the results of Jackson and Pelz, particularly in view of the rôle which such inhibitory efferents may play in the lung reflexes.

We have been unable to follow nerve branches from the cervical sympathetic into the lung as figured by Jackson and Pelz. The sym-

pathetic pulmonary branches described by them appear identical with the motor fibers from the brachial plexus to the striated muscle attached to the anterior and dorsolateral wall of the lung.

Stimulation of the central end of the cut cervical sympathetic may induce respiratory movements followed by lung contractions, provided the spinal cord and the vagi are intact. Or if the cervical sympathetic trunk is stimulated near its course past the brachial plexus, contractions of the striated lung muscle, previously referred to, may be produced by an escape of current to its motor fibers. These are the only motor effects on the lung that we have seen following the stimulation of the central end of the cervical sympathetic nerve, and neither are due to stimulation of sympathetic efferents.

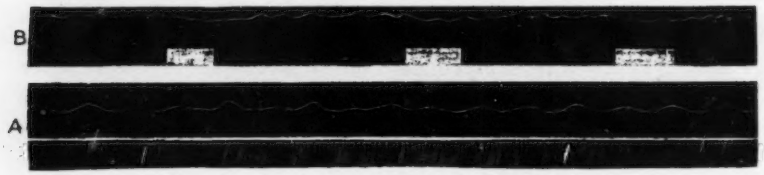

Fig. 23. Tambour tracings of the intrapulmonic pressure in the turtle. Animals decerebrated, fixed dorsal side down, plastron removed; stomach, liver and heart excised; vagi sectioned. Cannula in bronchus. *A:* Tracing showing a tonus rhythm in the lung independent of the vagi-medulla motor mechanism. *B:* Signal indicates stimulation of the central end of the cervical sympathetic nerve, showing slight inhibition (possibly reflex) of the peripheral lung tonus rhythm, developed after vagus section. Time, 5 second interval.

If the course of the sympathetic fibers to the lung in the reptilia is the same as in the amphibia and the mammals, these fibers should join the vagi in the neck or thorax and reach the lung via the pulmonary fibers of the vagi. We have stimulated the peripheral end of the cervical sympathetic nerve before its union with the vagus in very many preparations without any effect on the lung motor mechanism.

In one preparation only did we note any *inhibitory* effect on the lung from stimulation of the central end of the cervical sympathetic nerve. This preparation was decerebrated, fixed on the dorsal side, plastron removed, and eviscerated according to the method of Jackson and Pelz. A peripheral tonus rhythm appeared in the lung after section of the vagi. Tetanization (weak and strong) of the central end of the cervical sympathetic nerve induced some inhibition of this tonus

Fig. 24. Water manometer tracing of the intrapulmonic pressure in the turtle. Animal decerebrated, fixed dorsal side down; plastron removed; heart, liver, stomach and intestines excised; striated muscle on the anterior end of lung and its nerve connections left intact. *LL:* left lung; *RL:* right lung; *a*, spontaneous contraction (normal expiration) of the striated expiratory muscle on the surface of the lung, followed, during the respiratory pause, by prolonged tonus contractions of the lung musculature (asphyxia); *x*, section of the left vagus in the neck followed by cessation of the lung contractions, the respiratory contraction of the striated muscle on the lung persisting.

rhythm (fig. 23, *B*). Reflexes through the spinal cord were not excluded in this experiment.

The actual presence of sympathetic efferents to the reptilian lung is, therefore, an open question.

SUMMARY

1. Under normal conditions the external respiratory act inhibits the lung tonus by central action, and is followed by a contraction of the lung during the respiratory pause. These lung contractions are of central origin, the peripheral motor path being the vagi nerves (confirming Kahn and François-Franck).

2. The medullary center controlling the lung tonus and the lung contractions is not identical with the respiratory center, although normally associated with it in function in such a way that discharge from the respiratory center first depresses and then stimulates the lung motor center. The two centers are influenced in the same direction by asphyxial states, the lungs being put in a condition of incomplete tetanus by asphyxia, but one center may act, automatically or reflexly, without the other; and the lung motor centers are more profoundly influenced by afferent depressor nervous impulses (traumatic "shock").

3. The lung contraction developed during the respiratory pause is not a reflex depending on the muscular and other movements in the external respiratory act, as they persist after complete curarization, transection of the spinal cord in the neck, pithing the cord, or complete isolation of the lungs, save for the pulmonary vagi and blood vessels.

4. After section of the vagi a feeble tonus rhythm may appear in the lungs, but the strong contractions associated with external respiration are permanently abolished. Stimulation of the peripheral end of the vagi causes contractions and tetanus of the lungs, confirming the original observation of Bert. This vagus-lung action is unilateral. Stimulation of the peripheral vagus reveals no inhibitory action on the lung motor mechanism. Stimulation of the optic lobes or the medulla, the vagi being intact, causes lung contractions or incomplete lung tetanus (confirming Coombs). The lung tetanus is less complete than on direct stimulation of the peripheral end of the vagi, thus showing a central refractory state.

5. The physiological relation of the respiratory and the lung motor centers have a complete parallel in the relations of the activity of the swallowing center to the medullary mechanism controlling esophageal peristalsis. The action of the motor fibers of the vagi on the lung motor

tissues appears to be more direct and less complicated than the motor action of the vagi on the stomach, although there is some evidence of a tendency to an all-or-none response and rhythm in case of weak tetanization of the peripheral ends of the vagi even in the case of the lungs.

6. Inhibition as a primary act on the lung motor center in the medulla is produced by trauma to the vagi, stimulation of the central end of the inferior laryngeal nerve, and by strong stimulation of the central end of the pulmonary vagus. Trauma to the body causes a profound depression ("shock") of the lung motor center following an initial stimulation.

7. Reflex lung contractions or incomplete lung tetanus can be induced from stimulation of the sensory nerves of the respiratory tract (excepting the inferior laryngeal), that is by inflation, by deflation, or mechanical pressure on the lung of the opposite side, by weak tetanization of the pulmonary afferents, mechanical stimulation of the larynx and the nares. It is thus clear that the normal respiratory act by lung inflation and deflation will by itself induce a lung contraction reflexly. This afferent component from the lung is not necessary for the discharge of the lung motor center associated with the respiratory rhythm, but may act as a cumulative factor. The lung contractions and lung tetanus induced reflexly from mechanical stimulation of the posterior nares are particularly striking.

8. Mechanical and electrical stimulation of the alimentary tract (esophagus, gastric vagi, large and small intestine, rectum, cloaca) and the genito-urinary tract (urinary bladder, ureters, penis, prepuce, testes) induces reflex lung contractions or lung tetanus, the lung tetanus caused by stimulation of the cloaca, rectum and urinary bladder being particularly marked. Reflex lung contraction can also be evoked from stimulation of the gall bladder and the spleen.

9. Stimulation of the central ends of the visceral sympathetic nerves causes reflex lung contractions.

10. Stimulation (mechanical or electrical) of the cutaneous nerves, the cornea and the central end of the sciatic or brachial nerves induces reflex lung contractions or lung tetanus, depending on the strength of the stimulation.

11. The conclusions in regard to lung motor rhythm, its central and peripheral control, and the lung motor reflexes evoked from the head and neck region of the animal, apply both to the turtle and the snake. The lung reflexes from the viscera below the neck were not studied in the snake.

12. It would thus appear that the predominant reflex control of the lungs in these animals, at least under our experimental condition, is motor, thus differing entirely from the amphibia, where the predominating control (automatic and reflex) of the lung motor mechanism is inhibitory.

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STUDIES OF THE RESPIRATORY MECHANISM IN CARDIAC DYSPNEA

I. The Low Alveolar Carbon Dioxide of Cardiac Dyspnea

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It has been shown by many observers, working with various methods, Beddard and Pembrey (1), Porges, Leimdoerfer and Markovici (2), Peabody (3), Pearce (4)—that the alveolar carbon dioxide tension is usually found to be low in cardiac dyspnea. The causes and meaning of this phenomenon have never been clear. In cardiac dyspnea, in contradistinction to most conditions that are associated with a low alveolar CO_2, no proportionate reduction of the alkaline reserve of the blood has been found.

In 1917 one of us (5) studied the relation of the carbon dioxide tension of alveolar air to the bicarbonate concentration of venous plasma. A low alveolar CO_2-tension did not prove to be a constant characteristic of cardiac dyspnea. The alveolar CO_2 was sometimes normal. But it was always lower than normal in relation to the alkaline reserve of the blood as determined by the Van Slyke method. Van Slyke (6) found that in normal subjects the alveolar CO_2-tension maintained a fairly constant relation to the plasma bicarbonate. If the milligrams of CO_2 chemically bound in 1 cc. of plasma is multiplied by the constant 35, the result will be found to agree with the alveolar CO_2-tension (Haldane) expressed in mm. Hg. with about a 10 per cent variation. That is:

$$\text{(Alveolar } CO_2 \text{ in mm. Hg.)} \div \text{(mgm. } CO_2 \text{ chemically bound by 1 cc. of plasma} \times 35) = 100 \pm 10.$$

This observation we corroborated. That such a ratio should obtain in normal resting subjects seems reasonable. To a certain extent it

must represent the $H_2CO_3/NaHCO_3$ ratio, if the alveolar CO_2 can be assumed to be a measure of the arterial CO_2-tension and the bicarbonates of venous plasma an indication of the bicarbonates of whole blood.

In most normal resting subjects such assumptions will give rise to no serious errors. The difference between the carbon dioxide content of the arterial and the venous blood is not large and is comparatively constant. In pathological conditions which interfere with the general circulation or the ventilation of the blood in the lungs, a disturbance of these factors and consequently of the ratio may be expected.

In normal resting subjects the alveolar CO_2/plasma bicarbonate ratio varied between 0.90 and 1.10. In cardiac decompensation with dyspnea and in some very advanced pulmonary conditions we obtained ratios consistently below 0.85. To draw any definite conclusions as to the cause of the phenomenon was impossible. We suggested that it might be an expression of some defect of the normal mechanism for the elimination of carbon dioxide and pointed out the possibility of connecting this with the pulmonary changes which had been demonstrated by Siebeck (7), Peabody (8) and others.

Before any interpretation of the low alveolar CO_2[1] of cardiac decompensation is attempted it is obviously necessary to ascertain whether the method employed is applicable and whether the results obtained can be said to represent the true alveolar tension. The prel minary work was done with the Fridericia pipette (9). This has given rise to some criticism. Repetition with a more orthodox Haldane method has given substantially the same results. Although Pearce (4) has criticised the use of the Haldane method, observations by his own method are substantially in agreement with ours.

Siebeck (7), after a careful study of the respiratory mechanism in cardiac insufficiency, came to the conclusion that all determinations of the alveolar CO_2 were useless in this condition. According to Siebeck (7) the alveolar aeration in cardiac dyspnea is very imperfect, in consequence of which the expiratory air contains an excess of unchanged inspiratory air. Apparently he means that attempts to deduce the arterial CO_2-tension from the values obtained by the Haldane alveolar method are unwarranted. But it is perfectly possible to

[1] Although the reduction of the alveolar CO_2-tension is not absolutely constant, few patients fail to show it. In these few the carbon dioxide capacity of the plasma is distinctly high, while in most instances it is at or slightly below the normal level. It seems proper and simpler, for this reason, to speak of the low alveolar CO_2 of cardiac dyspnea.

consider the alveolar CO_2 on its own merits as a functional entity without any deductions about arterial CO_2-tension. However well grounded the anatomical conceptions of Haldane with regard to the origin of the alveolar air in the normal lung may be, it is quite conceivable that in pathological or physiological disturbances, conditions may be so altered that any anatomical term loses its original significance. Here a functional conception proves of greater value.

A normal expiration may be divided into two parts. The first part is practically useless from the standpoint of respiration; it merely serves to empty the dead space (the nose, mouth, pharynx, larynx, trachea and bronchi) of the room air with which it was filled by the last inspiration. In normal resting subjects the volume of this dead space is fairly constant, varying about an average of 130 cc. Behind this lies a mass of air of nearly constant gaseous composition throughout its whole extent and in close contact with the blood in the pulmonary circulation. This is the air which serves for the effective exchange of gases between the blood and the outside air, and it is a sample of this air that the Haldane method attempts to obtain.

The first object of these studies was to find out whether samples obtained by the Haldane method represented the effective respiratory air. We have employed other methods in order to determine whether they give results in agreement with the Haldane values.

Our studies have been confined to three methods: the Haldane (10), the Plesch (11) and the Henderson (12) venous CO_2. Pearce's (13) method has been omitted because its use in severe dyspnea presents considerable difficulties and also because it demands an amount of apparatus that renders it less adaptable as an ordinary clinical procedure.

THE HALDANE METHOD

The Haldane technique for obtaining alveolar specimens, although criticised for various reasons, is still considered the standard technique for the determination of the arterial CO_2-tension in normal subjects. It has not been generally adopted for clinical studies because of a popular opinion that it is difficult or impossible to obtain good samples in any but highly trained subjects. This we have not found to be the case. We are inclined to believe the observer needs more training than the subject.

In these studies we have adhered in all essential respects to the orthodox Haldane technique, introducing only slight modifications

which tend to diminish subjective errors. One of these is by no means original and consists of the introduction of a three-way brass stop-cock designed by Mr. G. F. Soderstrom and shown in figure 1. This makes it unnecessary for the patient to close the tube with his tongue. Furthermore, no attempt has been made to collect inspiratory and expiratory specimens, as Haldane advises. Instead, samples have been obtained from the end of a forced expiration begun as soon as possible after the completion of a normal inspiration. When the respirations

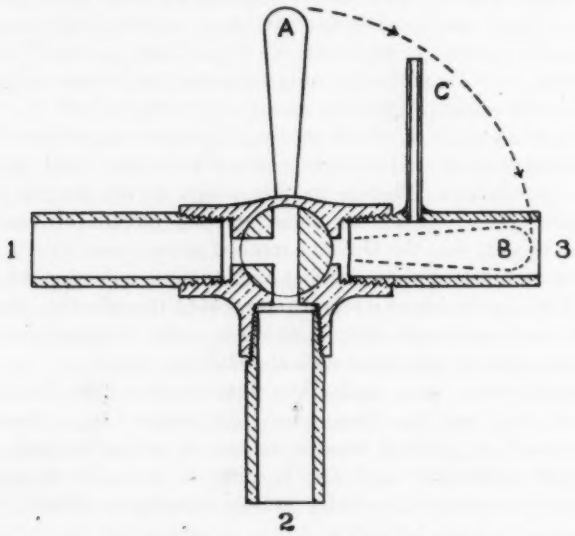

Fig. 1. Three-way stop-cock. *1*, tube for attachment of mouth-piece; *2*, tube leading to spirometer or left open to outside air; *3*, tube for attachment of Haldane tube, with side-arm *C*, to connect with gas sampling tube.

are rapid, as they are in cardiac dyspnea, it is almost impossible to turn the valve at the proper moment to differentiate inspiratory and expiratory alveolar air with any degree of certainty. The propriety of using an expiratory specimen also seems questionable. The prolongation of expiration during dyspnea may be equivalent to holding the breath for the duration of an extra respiration. We have tried to make the subjects force the air out rapidly enough so that the expiration is not considerably longer than a normal one. The specimens as obtained by this method are not all from expirations initiated at the same

point in the respiratory cycle, but at various points in the expiratory phase between full inflation and deflation of the lungs.

In detail the procedure is as follows: The rubber mouth-piece with the stop-cock and tube in place is first put in the patient's mouth with the stop-cock open to the air. He is encouraged to breathe through it to convince him that it will not "shut off his breath." After he has gained sufficient confidence the tube is removed from his mouth and a simple spring nose-clip applied to his nose. When he is sure he can breathe through his mouth alone without difficulty the mouth-piece is replaced in his mouth. He is then instructed how to deliver a sample on command and without altering his normal respirations. The sampling tube is then attached to the side-arm of the stop-cock. The operator stands at the right of the bed supporting the tube with his left hand, with his right on the handle of the stop-cock. When he feels that the breathing is normal and regular he tries to accustom himself to its rhythm, so that he may give the signal at the right moment. The signal is given and the stop-cock turned at the same moment. At the end of the forced expiration the cock is turned to the outside air again before the subject has had time to gasp for breath. The operator soon learns to know whether there has been a subjective error in the technique on his own part or that of the patient.

From an inexperienced subject we are accustomed to take several specimens. Although some of the first will occasionally be obviously too low, it is generally possible to get good agreement on the third or fourth attempt in even the most obtuse subject, as may be seen in tables 1 and 2. In a total of 48 observations on 25 patients, involving the collection and analysis of 127 samples, all but four patients gave duplicate samples that varied by 0.4 per cent or less, an accuracy that compares favorably with that found in trained subjects. Patients with cardiac dyspnea proved no exception to this rule. Three of the four patients (A. R., J. J. F. and D. W.) who gave unsatisfactory results on the basis of this criterion, exhibited Cheyne-Stokes breathing. The fourth (P. O. S.) was very ill, somewhat irrational and showed a slight respiratory irregularity.

The results obtained by the Haldane method are in accordance with those previously obtained with the Fridericia tube. The values are comparatively low and much lower than should be expected from the level of plasma bicarbonates. Two obvious criticisms of the method might be made:

1. That the volume of the expiration is too small to clear the patient's dead space.

TABLE 1

Variations in duplicate Haldane specimens in subjects without respiratory or cardiac disorders

SUBJECT AND CONDITION	ALVEOLAR CO_2	MAXIMUM OBSERVED VARIATION	MAXIMUM ACCEPTED VARIATION*	AVERAGE ALVEOLAR CO_2
	per cent			*mm.*
D. P. B., normal	6.16	0.22	0.22	43.1
	5.94			
	5.25	0.06	0.06	37.4
	5.31			
	5.72	0.02	0.02	40.6
	5.74			
	5.39	0.13	0.13	37.9
	5.26			
	5.16	0.24	0.24	37.6
	5.40			
	5.39	0.18	0.18	39.0
	5.57			
	5.60	0.00	0.00	38.7
	5.60			
	5.39	0.21	0.21	39.2
	5.60			
	5.45	0.05	0.05	38.8
	5.50			
	5.62	0.11	0.11	39.1
	5.51			
	5.32	0.34	0.34	38.6
	5.24			
	5.58			
J. P., normal	(5.28)	0.46	0.29	39.9
	5.64			
	5.74			
	5.45			
	5.94	0.09	0.09	41.6
	5.85			

TABLE 1—*Concluded*

SUBJECT AND CONDITION	ALVEOLAR CO_2	MAXIMUM OBSERVED VARIATION	MAXIMUM ACCEPTED VARIATION*	AVERAGE ALVEOLAR CO_2
	per cent			*mm.*
J. P., normal	5.88	0.26	0.26	40.5
	5.62			
	5.35	0.15	0.15	37.5
	5.20			
Capt., normal	6.24	0.07	0.07	44.4
	6.31			
W. S. M., normal	4.70	0.12	0.12	34.8
	4.82			
P. K., gastric neurosis	5.88	0.25	0.25	41.2
	5.61			
	5.86			
Jno. K., diabetes mellitus	4.24	0.16	0.16	30.1
	4.19			
	4.35			
	4.07	0.05	0.05	28.4
	4.06			
	4.02			
C. P., pernicious anemia	3.98	0.11	0.11	28.2
	3.91			
	4.02			
H. R., polycythemia	4.94	0.32	0.32	34.7
	5.11			
	4.79			

* Values in parenthesis in this and the following table have been discarded for the most part on the basis of internal evidence, only.

2. That the low values are produced by subjective errors; preliminary forced inspirations or gasping at the end of expiration.

To rule these out we attached the Haldane tube to a Tissot spirometer which was equipped with a calibrated recording device which will be described later. By this means we were enabled to obtain a graphic record of the respiration during the entire time that the stopcock was turned, and could at the same time measure the volume of the

TABLE 2

Variations in duplicate Haldane specimens with values for alveolar CO_2 and plasma bicarbonates in patients with cardiac disease

NAME AND DIAGNOSIS	ALVEOLAR CO_2	MAXIMUM OBSERVED VARIATION	MAXIMUM ACCEPTED VARIATION	AVERAGE ALVEOLAR CO_2	ALVEOLAR CO_2 CALCULATED FROM PLASMA BICARBONATE	DIFFERENCE BETWEEN CALCULATED AND OBSERVED ALVEOLAR CO_2	REMARKS
	per cent			*mm.*	*mm.*	*mm.*	
J. W., cardionephritic	4.71 4.75 4.76	0.05	0.05	34.6	39.7	5.1	Hypertension. No dyspnea, hyperpnea nor other signs of decompensation
J. A., cardionephritic	(5.21) 6.01 5.76 5.99	0.80	0.25	42.3	49.7	7.4	Hypertension, no dyspnea, cyanosis nor other signs of decompensation at rest
	4.38 3.98 4.25	0.40	0.40	30.0	41.5	11.5	Slight dyspnea and cyanosis. Lungs show râles at right base
A. J., shell shock	4.59 4.43 (4.03)	0.56	0.16	32.5	46.8	14.3	Effort syndrome. No organic cardiac nor pulmonary condition. Discrepancy probably due to over-ventilation
	4.86 4.78	0.08	0.08	33.6			

J. M. L., chronic cardiac	5.43	0.04	0.04	38.5			No symptoms nor signs of decompensation. Lungs clear
	5.39						
	5.11	0.24	0.24	37.2			
	5.35						
A. R., cardionephritic	3.96	0.82	0.82	30.6	31.9	1.3	Hypertension, signs of chronic uremia. Variations in alveolar samples probably due to Cheyne-Stokes breathing
	4.23						
	4.78						
	4.21						
R. W., chronic cardiac	5.69	0.23	0.23	41.0			No dyspnea, cyanosis nor other signs of decompensation
	5.90						
	5.67						
	5.78						
	5.79	0.33	0.33	42.4			
	6.12						
	6.10	0.42	0.42	44.7			
	6.22						
	6.52						
J. C., chronic cardiac	4.65	0.26	0.26	32.0			No dyspnea, cyanosis nor other signs of decompensation while at rest. The low alveolar values obtained in the first observation probably due to overventilation
	4.43						
	4.39						
	5.09	0.29	0.29	38.5	43.9	5.4	
	5.33						
	5.37						
	5.38						

TABLE 2—*Continued*

NAME AND DIAGNOSIS	ALVEOLAR CO_2	MAXIMUM OBSERVED VARIATION	MAXIMUM ACCEPTED VARIATION	AVERAGE ALVEOLAR CO_2	ALVEOLAR CO_2 CALCULATED FROM PLASMA BICARBONATE	DIFFERENCE BETWEEN CALCULATED AND OBSERVED ALVEOLAR CO_2	REMARKS
	per cent			*mm.*	*mm.*	*mm.*	
J. J. F., chronic cardiac	4.62 5.08 5.12 4.43	0.69	0.69	34.2	45.5	11.3	
D. W., cardionephritic	(3.08) 4.07 (3.22) 3.59	0.99	0.48	27.3	30.2	2.9	Aortic regurgitation with hypertension. Dyspnea and orthopnea with Cheyne-Stokes breathing. Slightly irrational. Great variations largely due to inadequate coöperation. Low values eliminated by graphic records. Dyspnea probably due to acidosis and not to cardiac disease
P. O. S., chronic cardiac	5.85 5.06 5.27 5.53	0.79	0.79	40.1	52.3	12.2	Extreme decompensation, dyspnea, orthopnea, and Cheyne-Stokes breathing
J. B., chronic cardiac	4.55 4.45	0.10	0.10	32.1	44.8	12.7	Moderate hyperpnea, some cyanosis. Slight edema. Lungs clear. No subjective dyspnea
	4.04 4.18	0.14	0.14	29.3			
	4.21 4.01	0.20	0.20	29.3			

	3.84	0.31	0.31	28.5			Moderate dyspnea and orthopnea while at rest. Some signs of fluid in right pleural cavity. Râles over base of left lung
	4.15						
W. W., cardionephritic	4.08	0.11	0.11	28.6	43.7	15.1	
	4.00						
	3.97						
	3.98						
	3.11	0.06	0.06	25.4			Considerable dyspnea and hyperpnea and orthopnea. Moderate cyanosis
	3.55						
	3.35	0.34	0.34	25.3	41.7	16.4	
	3.69						
	3.85	0.08	0.08	27.6	46.6	19.0	
J. D. B., chronic cardiac	3.82						
	3.90						
	3.89						
	4.51	0.30	0.30	32.2			
	4.62						
	4.64						
	4.34						
	4.59	0.08	0.08	32.8	48.0	15.2	Severe dyspnea, orthopnea, edema, right hydrothorax
J. R., chronic cardiac	4.56						
	4.64						
	5.10	0.21	0.21	35.9	46.9	11.0	Severe dyspnea and orthopnea, slight cyanosis. Slight dulness at base of right lung
	4.89						
C. D., chronic cardiac	4.43	0.32	0.32	32.5			
	4.75						
	4.53						

TABLE 2—*Concluded*

NAME AND DIAGNOSIS	ALVEOLAR CO_2	MAXIMUM OBSERVED VARIATION	MAXIMUM ACCEPTED VARIATION	AVERAGE ALVEOLAR CO_2	ALVEOLAR CO_2 CALCULATED FROM PLASMA BICARBONATE	DIFFERENCE BETWEEN CALCULATED AND OBSERVED ALVEOLAR CO_2	REMARKS
	per cent			*mm.*	*mm.*	*mm.*	
	5.36	0.58	0.17	38.7	47.8	9.1	Hypertension, auricular fibrillation, marked dyspnea and orthopnea. Some cyanosis. Deformity of right chest
	(4.95)						
	5.53						
	5.43						
	5.97	0.31	0.31	42.2	49.7	7.5	
Jos. C., cardionephritic	5.75						
	6.06						
	(5.78)	0.82	0.42	44.9	52.2	7.3	
	6.22						
	6.60						
	6.31						
	6.18						
	4.01	0.36	0.36	27.4	47.6	20.2	Extreme dyspnea, orthopnea, cyanosis and edema, right hydrothorax, râles over remainder of lungs
S. I., chronic cardiac	3.65						
	3.91						
	4.21	0.09	0.09	29.7	40.9	11.2	Considerable cyanosis, orthopnea, and dyspnea. Signs of fluid in right pleural cavity
D. O. C., chronic cardiac	4.12						
	3.61	0.22	0.22	26.5			Cyanosis and dyspnea more marked
	3.83						

D. O. C., chronic cardiac	3.61	0.38	0.38	26.7			Condition unchanged
	3.99						
	3.67						
	3.70	0.87	0.36	26.6	38.2	11.6	Pleural fluid has increased. Dyspnea more marked
	3.92						
	(4.43)						
	3.56						
	3.97	0.36	0.36	23.6			Fluid in both pleural cavities
	3.61						
	3.52	0.30	0.30	26.2			Condition unchanged
	3.82						
	3.70						
J. M., chronic cardiac	3.52			25.0	40.9	15.9	Extreme cyanosis. Moderate dyspnea, considerable hyperpnea, right hydrothorax
	4.87	0.16	0.16	34.8	52.0	17.2	No dyspnea, moderate hyperpnea, cyanosis still marked. Hydrothorax diminished
	5.03						
J. K., chronic cardiac	3.26	0.23	0.23	22.0	37.8	15.8	Extreme cyanosis, slight dyspnea, considerable hyperpnea, few râles scattered over both lungs
	3.13						
	3.03						
	3.03						
	4.24	0.62	0.62	32.5			Dyspnea gone, cyanosis slight, still some hyperpnea. Lungs clear
	4.86						
	4.56						
C. C., chronic cardiac	3.95	0.27	0.27	27.4			Marked cyanosis. Little dyspnea. No orthopnea. Considerable hyperpnea
	3.68						
	3.91						

TABLE 3

Relation of alveolar CO_2 to volume of expiration

SUBJECT	VOLUME OF EXPIRATION	ALVEOLAR CO_2
	cc.	*per cent*
J. C., chronic cardiac compensated	1016	5.09
	823	5.33
	807	5.37
	790	5.38
W W., chronic cardiac decompensated	797	4.08
	864	4.00
	615	3.97
	665	4.35
	385	4.32
R. W., chronic cardiac compensated	710	5.90
	452	5.67
	645	5.78
	758	6.10
	651	6.22
	516	6.52
J. D. B., chronic cardiac decompensated	1081	4.51
	1290	4.62
	758	4.64
	986	4.34
A. R., cardionephritic. Periodic breathing	505	3.96
	535	4.23
	430	4.78
	505	4.21
D. W.,* cardionephritic. Periodic breathing	(758	3.08)
	677	4.07
	(629	3.22)
	952	3.59

* See figure 2.

expiration. Table 3 shows the values obtained from six experiments done in this way. From the first five experiments it is evident that the expiratory volume is sufficient to clear completely any but an enormously increased dead space. If the dead space were increased to this

degree, however, the alveolar CO_2-tension should vary with the expiratory volume. This relation does not obtain. In only one instance, the second observation on R. W., is any such relation even suggested, and in this case the total variation is only 0.23 per cent.

In none of these cases is there any indication in the graphic records of inspiratory activity during the time that the stop-cock was open. That the method is capable of showing such subjective errors is demonstrated in the record of D. W. (fig. 2). This patient presented symptoms of uremia with Cheyne-Stokes respiration. His tracings show that the low values obtained from the first and third samples were due

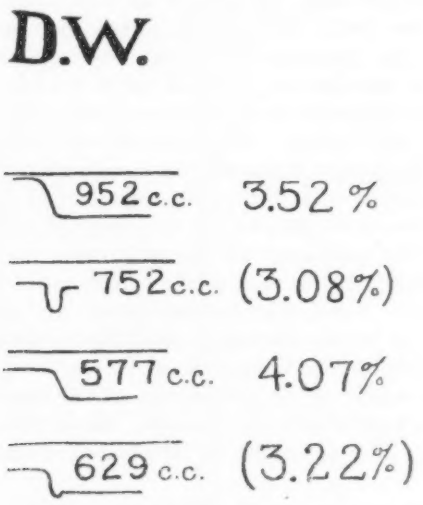

Fig. 2

to inspirations while the valve was open and before the samples had been withdrawn. The discrepancy in the two remaining values seems to depend on the fact that one was obtained during an apneic, the other during a dyspneic period.

The low alveolar CO_2 is not due to subjective errors on the part of the patient nor to any considerable increase in the volume of the dead space.

The alveolar CO_2 after rebreathing. One of the most striking characteristics of decompensated cardiac patients is the intolerance to an increase of CO_2 in the inspired air (14).

It has been shown by Haldane (15) and others that when a person rebreathes air the alveolar CO_2-tension and the ventilation increase as the CO_2 in the inspired air rises. When the alveolar CO_2-tension has risen to a certain point the patient becomes extremely dyspneic and uncomfortable. This we may call the point of intolerance to CO_2. If the alveolar CO_2 be low in cardiac dyspnea at rest it seems reasonable to suppose that it should also be relatively low after rebreathing to the point of intolerance.

For the rebreathing experiments a 100-liter Tissot spirometer, accurately balanced and calibrated at all levels, was employed. To separate the inspired from the expired air a two-way T-valve of the Douglas type was used. Between the mouth piece and this T-valve was interposed the three-way brass stop-cock described above. The opening with the side-arm was, as usual, fitted to a long, wide-bore rubber tube for the collection of alveolar specimens. The other arm was connected with the T-valve. (The total instrumental dead space was about 50 cc.) In this way it was possible to collect specimens of alveolar air during the course of a rebreathing experiment by merely turning the stop-cock during expiration and directing the patient to breathe out forcibly. The inspiratory air was withdrawn from the spirometer through the opening in the top usually employed for the insertion of the thermometer. Samples of the inspiratory air were drawn from this tube near the T-valve through a small rubber side arm. Graphic records of the respirations were obtained by means of a pen attached to the counter-weight of the spirometer. As it moved in a vertical plane only, direct calibration was possible. Simultaneous time records were obtained. The apparatus is represented diagrammatically in figure 3.

The spirometer was filled with 20 liters of room air for each experiment. A larger amount was found to prolong the experiment unduly and to introduce a considerable element of fatigue. Smaller amounts rendered the succession of events too rapid to permit the introduction of all the necessary procedures and accurate analysis of the results obtained.

The minute volume attained in the rebreathing experiments was calculated from the average tidal air and the respiratory rate during the last half-minute of the experiment, except in one or two cases where the limit of tolerance was reached so rapidly that it was necessary to use a shorter terminal period for purposes of calculation. Of course, assuming that the minute volume increases continuously throughout

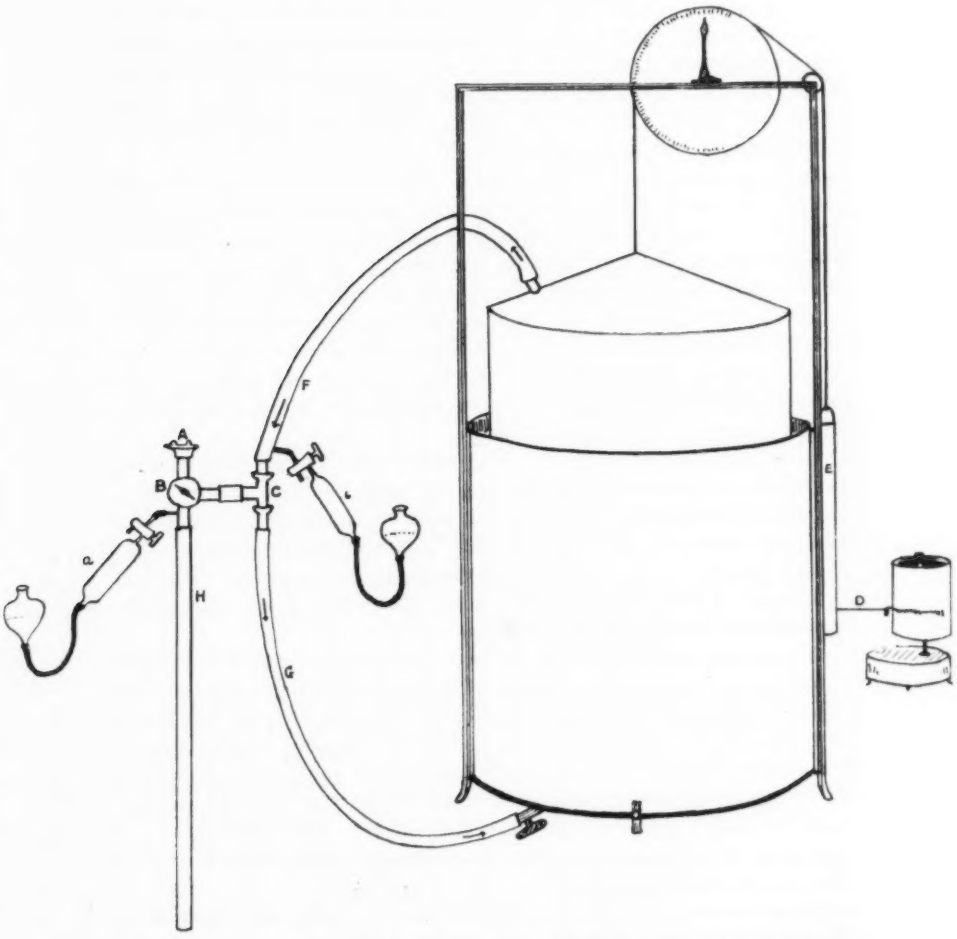

Fig. 3. *A*, mouth-piece; *B*, 3-way stop-cock; *C*, Douglass valve; *F*, inspiratory tube; *G*, expiratory tube; *E*, counterweight of spirometer; *D*, recording pen; *H*, Haldane tube; *a*, sampling tube for alveolar air; *i*, sampling tube for inspiratory air.

the course of the experiment, the values obtained in this way must be somewhat too low. On the other hand, the respirations never become absolutely regular, and calculations based on too small a number will be subject to considerable error. In rebreathing so large a volume as 20 liters the respiratory increase is sufficiently gradual to permit the use of the last half-minute, in the majority of instances, with the introduction of no significant error.

After a satisfactory determination of the resting alveolar CO_2 and minute volume had been made, a rebreathing experiment was begun. The patient was urged to continue as long as he felt able. When he had reached the limit of tolerance the valve of the three-way stop-cock was opened to the Haldane tube during an expiration. The patient was told to breathe out forcibly and the valve was again closed before the following inspiration. The patient was at once disconnected from the apparatus and the alveolar sample removed for analysis. The second operator at the same time removed a sample from the inspiratory tube.

Of course, the coördination and coöperation of the subject were necessary and there were opportunities for mistakes. Altogether eleven successful experiments were made on two normal subjects; one out of two was successful in a patient with a gastric neurosis; one in shell shock; three in two compensated cardiacs; and five out of seven attempted in four patients with cardiac decompensation. The results appear in summarized form in table 4.

A very striking difference is apparent at once between the decompensated cardiac cases and the others. The former were unable to tolerate as much CO_2 in the inspired air and their alveolar CO_2 did not rise to as high a level. This was due to no lack of will power on the part of the cardiacs because in one or two cases they continued rebreathing to the point of exhaustion, while none of the compensated subjects went beyond a state of moderate discomfort. The alveolar CO_2 at the point of intolerance is therefore lower in decompensated cardiacs than it is in normal persons.

With the exception of A. J., the shell shock patient, the height of the alveolar CO_2 at which intolerance was reached bore a general relation to the preliminary alveolar CO_2-tension. In this one case the low resting alveolar CO_2 was due to over-ventilation. This was clearly shown by the fact that his initial reaction to rebreathing was a reduction of the minute-volume, instead of an increase.

TABLE 4

The effect of rebreathing on the alveolar CO_2

NUMBER AND NAME	RESTING ALVEOLAR CO_2	AT END OF REBREATHING EXPERIMENT		DIAGNOSIS AND REMARKS
		Inspiratory air CO_2	Alveolar CO_2	
	per cent	*per cent*	*per cent*	
1. D. P. B.		8.36	8.52	Normal adult. Continued rebreathing to point of considerable discomfort
	6.05	8.01	8.16	
		7.93	8.21	To discomfort
	5.28	8.06	8.30	To discomfort
	5.73	7.84	7.95	To slight discomfort
		6.86	7.53	To slight discomfort
2. J. P.		7.90	8.32	Normal adult. To considerable discomfort
		7.95	7.98	To extreme discomfort
		6.90	7.27	To discomfort
		6.86	7.05	To considerable discomfort
3. P K.	5.78	6.61		Gastric neurosis
	5.50	6.07	6.85	To moderate discomfort. No exhaustion
4. T. deC.	5.50	5.90	7.30	Chronic cardiac valvular disease, compensated
	5.70	6.59	7.27	Rebreathed to point of moderate discomfort
5. J. M. L.	5.23	7.54	7.92	Chronic cardiac. Compensated. Continued rebreathing to point of considerable discomfort
6. A. J.	4.51	6.26	6.30	Shell shock with effort syndrome.
	4.72	6.30	6.89	To moderate discomfort only
7. J. A.	5.92	5.74	6.36	Chronic cardiac, valvular disease, compensated while at rest. Rebreathed to point of considerable discomfort with some exhaustion
		4.52	7.34	
8. J. B.	4.50	3.70		Chronic cardiac valvular disease. Moderate dyspnea while at rest. In the first two experiments continued only to mild discomfort. In the last experiment considerable discomfort. Somewhat exhausted
	4.50	3.92	5.55	
	4.11	5.17	6.26	

TABLE 4—*Concluded*

NUMBER AND NAME	RESTING ALVEOLAR CO_2	AT END OF REBREATHING EXPERIMENT		DIAGNOSIS AND REMARKS
		Inspiratory air CO_2	Alveolar CO_2	
	per cent	*per cent*	*per cent*	
9. Jos. C....	5.93	3.88	6.68	Cardio-nephritic with cardiac decompensation. Considerable dyspnea and hyperpnea. Continued to point of considerable discomfort. Somewhat exhausted
10. C. D....	5.00	2.13	5.10	Chronic cardiac, valvular disease with marked decompensation. Continued to point of marked exhaustion
	4.57	2.89		
11. D. O. C.	4.17	2.94		Chronic cardiac, valvular disease with decompensation. Continued rebreathing to point of discomfort with some exhaustion
		2.53	5.72	

In cardiac dyspnea, then, the alveolar CO_2 is low at the point of intolerance. The relation of the alveolar CO_2 at this point to the resting alveolar CO_2 is similar to that found in normal persons. This is further evidence that the air in the lungs in cardiac dyspnea really presents a diminished CO_2-tension.

THE PLESCH METHOD

Modifications of the Plesch method of obtaining samples of alveolar air have been employed extensively in cardiac disease and other pathological conditions by numerous workers. Both Porges (2) and Peabody (3) used it for their studies on cardiac dyspnea. With this method, the subject rebreathes a limited volume of air, usually 600 to 1000 cc. a number of times, usually from 5 to 10, in a period of time usually between 20 and 30 seconds, which is supposed to be less than the duration of a single complete circulation of the blood. With normal resting subjects it gives values that lie a little higher than those obtained by the Haldane method and is assumed to represent the tension of CO_2 in the venous blood.

Usually the rate and depth of the respirations and the duration of rebreathing can be varied within rather wide limits with only a slight

variation in the analyses obtained. This might reasonably be expected even if the theoretical basis of the method were entirely wrong. It has been shown that in normal subjects at rest, lung volume, carbon dioxid output, arterial CO_2-tension and venous CO_2-tension vary within narrow limits absolutely and in relation to one another.

The assumption that such an empirical method is equally applicable to the study of a condition in which all these factors are greatly disturbed, is hardly justifiable.

We have made a few observations on normal subjects and on patients with cardiac disease (see table 5) in which we tested the effect of varying

TABLE 5

Results of varying time and number of respirations on Plesch-alveolar CO_2

	NORMALS				J. M. L. COMPENSATED CARDIAC	DECOMPENSATED CARDIACS					
	D. P. B.			J. P.		S. I.	D. O. C.		W. W.	J. B.	
5 respirations in 25 seconds	6.17	6.04	5.24	6.29	6.08	4.48	4.85	5.41	4.70	5.03	4.82
10 respirations in 25 seconds	6.53	5.97	5.90	6.22	6.76	4.62	4.92	5.88	5.41	5.14	5.53
5 respirations in 35 seconds	6.43	6.35	5.89	6.34	6.90			5.99	5.67	5.63	5.81
10 respirations in 35 seconds	6.34	6.41	5.88	6.43	6.92	4.70		6.29	5.99	5.50	
Average value	6.37	6.19	5.73	6.32	6.67	4.60	4.89	5.89	5.44	5.33	5.17
Maximum variation	0.36	0.44	0.66	0.21	0.84	0.22	0.07	0.88	1.29	0.60	0.99
Haldane alveolar CO_2	5.28	5.33		5.61	5.41	3.86	3.72	3.75	4.34	4.11	4.11
Difference between Plesch and Haldane	1.09	0.86		0.71	1.26	0.74	1.17	1.99	1.10	1.22	1.06

the time and rate of rebreathing within certain limits. The time limits chosen were 25 and 35 seconds; the number of breaths 5 and 10. The apparatus used was essentially the same as that recommended by Peabody (16): a three-way brass stop-cock described above, which connected the subject either with the outside air or a rebreathing bag containing 1000 cc. of room air. The bore of the valve and tubing was 1.75 cm., the instrumental dead space, including the rubber mouthpiece, 30 cc. Rebreathing was always begun after a forced expiration and the patient was directed to make a maximum respiratory effort with each breath.

In the case of J. P. the total difference obtained within the limits of variation of time and number of respirations employed was 0.21 per cent. In D. P. B. the differences were greater: from 0.36 to 0.66 per cent. Moreover, in one experiment on the latter (no. III) it appears that the duration of the experiment has less influence than the number of respirations. In the cardiac patients studied the differences were slightly larger, in one case 1.29 per cent. Again variations in the number of respirations appear almost as important as variations in time. One would be rather at a loss to know which values to accept under these conditions.

Of course 35 seconds and 10 breaths are both in excess of the limits usually employed. The objection may be raised that we have not limited the element of time and the number of breaths sufficiently. To us it seems essential to determine whether limitation of experimental factors produces an equivalent limitation of variation in all subjects. One is not justified in producing an apparent constancy in results by an arbitrary limitation of experimental variations.

THE HENDERSON-LAURENS METHOD

Y. Henderson (12) has recently published a method for the determination of the venous CO_2-tension. It does not differ in principle from previous methods, but demands less effort and intelligence on the part of the subject and is therefore more applicable to clinical studies. It depends on the principle of intermittent rebreathing. Laurens (17) has pointed out that it is necessary to regard certain precautions in rebreathing because diffusion of CO_2 is more perfect during respiratory motions than it is while the chest is motionless. Our technic has been modified, therefore, to meet his requirements.

The apparatus used was the same as that employed in the Plesch studies. The rebreathing bag was filled with about 2000 cc. of expiratory air. In most cases a second observation was made in which the bag was filled with a mixture of air with 6.5 to 10 per cent CO_2. While the patient was breathing room air quietly through the valve, he was ordered to give a maximum expiration. When his lungs were completely deflated the stop-cock was turned. He then filled his lungs with a mixture from the bag by a deep inspiration, retained the air in his lungs about 10 seconds and expired into the bag forcibly. The stop-cock was then turned to the room again and he resumed normal respirations. After a sufficient interval to permit the respirations to return

to normal the same procedure was repeated. After each respiration the mixture in the bag was tested for CO_2. The rebreathing was continued until analyses after successive respirations showed that the CO_2-tension had reached a practically constant level. In normal subjects this level is reached after about 7 rebreathings and the level attained in rebreathing expired air and CO_2 rich mixtures is the same.

The results of these studies are shown in table 6. Not all of the experiments are entirely satisfactory; but a more or less constant level is reached in cardiac subjects as well as in normals.

There is a surprisingly close agreement between the venous alveolar values obtained by the Henderson-Laurens method and the average of the values obtained by the Plesch method. The application of the Plesch method, in the simple form usually employed, to the physiologic study of cardiac disease, seems hardly warranted. The limitation of the number of respirations and the duration of rebreathing is more or less arbitrary and based on the study of normal subjects only. The use of an average value obtained from a series of observations in which both time and number of respirations has been varied seems preferable. In normal and cardiac subjects values so obtained agree with those obtained by at least one other venous method.

The difference between the Henderson and the Haldane alveolar CO_2 is greater in subjects with cardiac dyspnea than in normal persons or cardiac patients without dyspnea. In spite of this the actual values found by the Henderson method in cardiac dyspnea are slightly lower than normal. This is again evidence that the carbon dioxide tension of the air in the lungs is reduced in cardiac dyspnea.

It is not possible to argue that the difference between the Henderson and the Haldane alveolar CO_2 represents the difference of CO_2-tension between arterial and venous blood. The Haldane values can not be interpreted as a measure of the arterial CO_2-tension until the criticisms of Siebeck have been answered. The only way to answer them is by the direct determination of the arterial CO_2-tension. The objections to the application of alveolar methods to the determination of the carbon dioxid tension of venous blood are even greater. Christiansen, Douglas and Haldane (18) have pointed out that direct determination of the venous carbon dioxid tension by these methods is impossible. The peculiar effect of oxygen on the carbon dioxid dissociation curve of the blood necessitates the introduction of a correction for the oxygen unsaturation of venous blood. An average correction can be applied in the case of normal persons without any considerable error. In

TABLE 6

Comparison of Henderson-Laurens with Haldane method and its application to cardiac dyspnea

SUBJECT AND CONDITION	REBREATHING EXPIRED AIR		REBREATHING CO_2-AIR MIXTURE			CALCULATED VENOUS ALVEOLAR CO_2	PLESCH ALVEOLAR CO_2	HALDANE ALVEOLAR CO_2	DIFFERENCE BETWEEN HENDERSON AND HALDANE	ALVEOLAR CO_2 CALCULATED FROM PLASMA BICARBONATE
	Number of rebreathings	CO_2 found in bag	Mixture rebreathed CO_2	Number of rebreathings	CO_2 found in bag					
		per cent	*per cent*		*per cent*	*mm.*	*mm.*	*mm.*	*mm.*	*mm.*
D. P. B., normal	2	5.25				44.9	45.8	37.9	6.9	
	3	5.74								
	4	6.17								
	5	6.28								
	4	5.69				45.1	45.4	37.6	7.5	
	5	6.21								
	6	6.26								
	7	6.38								
			6.64	6	5.79	43.4		39.0	4.4	
	7	6.14		7	5.82					
	8	6.07		8	5.86					
	9	6.13		9	6.01					
			7.55	6	5.97	42.7		39.3	3.4	
	7	5.95		7	5.88					
	8	6.23		8	5.93					
	9	6.06								
	7	5.80	10.02	5	5.99	41.9		39.2	2.7	
	8	5.84		6	6.03					
	9	5.79		7	5.91					

J. P., normal	2	6.13				43.8	45.0	39.9	3.9	
	3	6.13								
	5	6.20								
			10.34	3	7.02	48.6				
				4	7.01					
	7	6.67		5	6.93					
	8	6.83		6	6.86					
	9	6.83		7	6.77					
	8	6.14	6.96	5	6.34	44.8				
	9	6.23		6	6.28					
	10	6.21		7	6.34					
			7.14	5	5.99	41.9		42.3	4.0	
	7	5.82		6	5.98					
	8	5.76		7	5.95					
J. A., chronic cardiac compensated	4	6.45				46.6		42.3	4.3	49.7
	5									
	6	6.53								
	7	6.52								
J. C., chronic cardiac compensated	7	5.59	10.0	7	6.53	44.9		37.7	7.2	
	8	5.75		8	6.45					
	9	6.00								
J. M. L., chronic cardiac compensated	3	6.25				48.4	47.5	38.5	9.9	
	4	6.66								
	5	6.74								
			7.64	7	6.44	47.8		42.4	5.4	
R. W., chronic cardiac compensated	8	6.44		8	6.72					
	9	6.52		9	6.72					

TABLE 6—*Concluded*

SUBJECT AND CONDITION	REBREATHING EXPIRED AIR		REBREATHING CO_2-AIR MIXTURE			CALCULATED VENOUS ALVEOLAR CO_2	PLESCH ALVEOLAR CO_2	HALDANE ALVEOLAR CO_2	DIFFERENCE BETWEEN HENDERSON AND HALDANE	ALVEOLAR CO_2 CALCULATED FROM PLASMA BICARBONATE
	Number of rebreathings	CO_2 found in bag	Mixture rebreathed CO_2	Number of rebreathings	CO_2 found in bag					
		per cent	*per cent*		*per cent*	*mm.*	*mm.*	*mm.*	*mm.*	*mm.*
J. B., chronic cardiac decompensated	2	5.07				38.9	38.4	29.3	9.6	
	3	5.48								
	4	5.43								
	5	5.25								
Jos. C., chronic cardiac decompensated	4	6.11				45.2		38.7	6.5	47.8
	5	6.35								
	6	6.39								
	7	6.30								
	6	6.77	8.92	5	6.99	48.9		44.9	4.0	52.2
	7	6.34		6	7.06					
	8	6.40		7	6.95					
W. W., chronic cardiac decompensated	7	5.64	6.44	7	5.36	38.7		28.6	10.1	43.7
	8	5.45		8	5.33					
	9	5.43		9	5.59					
D. O. C., chronic cardiac decompensated	3	5.29				40.6	42.1	26.7	13.9	38.2
	4	5.71								
	5	5.56								
	6	5.74								
	7	4.89	7.79	7	5.43	36.0		25.3	10.7	
	8	4.92		8	5.15					
	9	5.04		9	5.07					
Averages (normal subjects and compensated cardiacs)						45.0		39.2	5.4	
Averages (decompensated cardiacs)						41.4		32.3	9.1	

patients with cardiac decompensation, however, the oxygen unsaturation of the venous blood is much greater (19) and more variable. The use of a standard correction factor may therefore involve considerable error.

SUMMARY AND CONCLUSIONS

The Haldane method of obtaining alveolar air has been employed in the study of a series of cardiac patients with dyspnea with no greater variation in results than is found in studies of trained normal subjects. The carbon dioxid tension of alveolar air thus obtained has been found consistently low in comparison with the carbon dioxid capacity of venous plasma. The comparatively low values are not due to technical or subjective errors nor to any considerable increase in the volume of the dead space. The patient with cardiac decompensation maintains his alveolar CO_2 at a lower level than does the normal and the level to which he will permit it to rise under the influence of rebreathing is proportionately reduced.

The Plesch method gives variable results according to the number of respirations and the duration of rebreathing. If, however, an average of a series of observations in which these factors have been varied is employed the results agree with those given by the Henderson method for venous alveolar CO_2. The values found by these methods are somewhat lower in decompensated cardiac subjects than in normal persons; but are high in relation to the values given by the Haldane method.

No attempt has been made to translate alveolar CO_2-tension into terms of arterial or venous CO_2-tension. The alveolar air has been considered entirely from a functional standpoint as that portion of the air in the lungs which is available for the exchange of gases between the blood in the pulmonary circulation and the outside air. If the term "alveolar air" is used in this sense, it may be said that the alveolar CO_2-tension of subjects with cardiac dyspnea is low in comparison with the carbon dioxid capacity of the plasma. As the latter is variable, but seldom abnormally high, the alveolar CO_2-tension is usually not only relatively but absolutely diminished.

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STUDIES OF THE RESPIRATORY MECHANISM IN CARDIAC DYSPNEA

II. A Note on the Effective Lung Volume in Cardiac Dyspnea

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That the vital capacity of the lungs is reduced during cardiac decompensation is a well-established fact (1), (2). A few experiments have been conducted to find out whether this reduction is associated with a change in the total air containing space of the lungs and to ascertain the effect of such a change on the functional efficiency of the respiratory mechanism.

METHODS

The problem has been approached in two distinct ways: *a*, by the application of the Lundsgaard (3) method for measuring the lung volume by rebreathing oxygen; *b*, by a study of the effect of continuous rebreathing of air on the volume of the tidal air and the comparison of the latter with the vital capacity.

The lung volume of a few normal and pathological cases was measured by the Lundsgaard (3) method of rebreathing oxygen. A graphic record of the preliminary respirations and the vital capacity was obtained with a Tissot spirometer by means of a combination of valves similar to that used for rebreathing experiments and described in the preceding paper (4). A rebreathing bag containing a measured amount of oxygen was attached in place of the Haldane tube. In all cases the subject commenced rebreathing from the position of complete expiration. The volume of the residual air was calculated from the gas mixture in the bag at the end of the observation. The volume of the vital capacity was obtained from the graphic record. The values thus obtained were compared with those obtained by the Lundsgaard (3) method of chest measurement.

TABLE 1

Vital capacity and lung volume

NAME AND CONDITION	DATE	VITAL* CAPACITY	RESIDUAL AIR*	LUNG* VOLUME	METHOD OF DETERMINATION			REMARKS
					Volume of O_2 rebreathed	Number of respirations	Time of rebreathing	
		cc.	*cc.*	*cc.*	*cc.*		*seconds*	
1. D. P. B., normal	*Lundsgaard measurements*	*3332*†*	*1478*†*	*4810*†*				Low Lundsgaard measurement probably faulty and due entirely to excessively short sternum
	v/19	4429	1662	6091†	3000	7	18	
	v/21	4328	1551	5879†	3000	7	15	Ratio V. C./Surface Area = 2.73
	v/22	4239	1715	5954†	2050	7	17	
		4284	1632	5916†	2010	7	15	
2. J. P., normal	*Lundsgaard measurements*	*3704*	*1609*	*5313*				
	v/22	3772	1621	5393	3000	7	17	
		3876	1723	5599	2000	7	17	
3. J. C., chronic cardiac	*Lundsgaard measurements*	*2980*	*1460*	*4390*				Young boy of 18 with early rheumatic endocarditis Compensated at rest
	vi/10/19	2345	1560	3905	2070	7	18	No dyspnea nor hyperpnea at rest. Lungs clear
		2432	1515	3947	2070	7	18	

	Lundsgaard measurements	*2930*	*1460*	*4390*				Chronic cardio-nephritic. Hypertension. Cardiac hypertrophy. Blood pressure 210
4. J. A., chronic cardiac	v/16/19.....	2430						No dyspnea nor hyperpnea while at rest. Lungs clear
	vi/7/19.....	1242	1214	2456	2020	7	19	Some hyperpnea even when at rest in bed. Lungs clear except showers of râles at right base
		1329	1250	2579	1500	7	17	
		1418						
	Lundsgaard measurements	*3640*	*1740*	*5380*				At time of examination was found to have very little hyperpnea. Also had a reduction of the plasma bicarbonate. The hyperpnea was probably due to the reduction of the alkaline reserve and not to cardiac factors. Chest clear. Periodic breathing
5. A. R., chronic cardiac	vi/27/19.....	1489	1744	3233	1510	7	17	
		1789						
	Lundsgaard measurements	*4698*	*2315*	*7013*				Moderate hyperpnea. Some dulness and râles at extreme bases on both sides
6. W. W., chronic cardiac	vi/24/19.....	1174	2320	3494	1500	7	14	
	vi/25/19.....	1452	2190	3642	1535	7	20	

TABLE 1—*Concluded*

NAME AND CONDITION	DATE	VITAL* CAPACITY	RESIDUAL AIR*	LUNG* VOLUME	METHOD OF DETERMINATION			REMARKS
					Volume of O_2 rebreathed	Number of respirations	Time of rebreathing	
		cc.	*cc.*	*cc.*	*cc.*		*seconds*	
7. R. W. chronic cardiac	*Lundsgaard measurements*	*3930*	*1870*	*5800*				No dyspnea when at rest. Some impairment of resonance at extreme right base
	vi/23/19.....	1714	1264	2978	2070	7	17	
		1064	1244	2308	2000	7	17	
	vi/24/19.....	1869						
	vi/30/19.....	2080	1091	3171	2040	7	17	
8. D. O. C., chronic cardiac	*Lundsgaard measurements*	*3540*	*1800*	*5340*				
	iv/29/19.....	1303						Marked dyspnea when at rest. Some signs of fluid at right base
	vi/2/19.....	920	757	1677	2020	7	Very rapid	Some fluid in right chest
		985	799	1784	1040	15	17	
	vi/6/19.....	1193	873	2066	1060	15	Very rapid	Dyspnea more marked. Fluid to angle of right scapula; 1450 cc. removed just after experiment
	vi/9/19.....	1068	887	1955	990	12	17	Dyspnea less marked. Fluid above angle of right scapula. Some dulness at extreme left base
		1132	861	1993	1000	15	17	

* In each case the values for the normal lung volume as determined by the Lundsgaard method of chest measurement are reported first, in italics. Below them appear the values obtained by the rebreathing method.

† The great discrepancy between the observed and the calculated lung volumes of DPB seems to be due to a very short sternal measurement. The relation between his vital capacity and surface area is quite normal, 2.73. In the light of the work of Dryer and that of West it appears that the surface area is a better criterion from which to calculate the vital capacity. Unfortunately we have not sufficient data to permit recalculations on this basis.

The apparatus and method employed in the rebreathing experiments were described in the first paper of this series (4). By a study of the tidal air of normal subjects and cardiac patients after the continuous rebreathing of air from a spirometer, we hoped to gain some information on the effect of the reduction of vital capacity on the functional efficiency of the respiratory mechanism.

RESULTS

The results of the lung volume determinations are collected in the first three columns of table 1. In each case the normal lung volume, as calculated by the Lundsgaard (3) method of chest measurement is reported first, in italics. Below it appear the values obtained from the rebreathing experiments. In the fourth, fifth and sixth columns are given the conditions of the experiments: the volume of oxygen taken in the rebreathing bag; the number of respirations and the duration of the rebreathing.

The first two subjects were normal. The third had chronic cardiac valvular disease without decompensation. His vital capacity, residual air and lung volume were almost normal. Number 4, at the first observation, in the absence of dyspnea, showed only a slight reduction of the vital capacity. Three weeks later, with a recurrence of dyspnea, his vital capacity was found to be only half as large. His residual air was not far from normal. Unfortunately his residual air was not determined at the time of the first observation.

Number 5, A. R., had hypertensive nephritis with some edema and signs of uremia: drowsiness and Cheyne-Stokes breathing. He showed no considerable hyperpnea, although his plasma bicarbonate was reduced. His chest was entirely clear. His vital capacity was very small but his residual air practically normal.

The last three were decompensated patients with dyspnea and showed very low vital capacities. The volume of the residual air was also considerably below normal in the last two. With the exception of the last patient, who had a massive hydrothorax, the physical signs found in the chest were insignificant in comparison with the diminution of lung volume.

These results indicate that, in patients with cardiac dyspnea, the total volume of air in the lungs which can be detected by the usual methods is considerably less than that found in normal persons. The largest part of the reduction in lung volume is due to a diminution of the vital capacity. The residual air is unchanged or slightly reduced.

The results of the rebreathing experiments are given in table 2. The subjects are arranged from above downward according to the magnitude of their vital capacities, which appear in column 1. In column 2 is given the normal vital capacity as calculated from the Lundsgaard (3) chest measurements. In column 3 is shown the average resting tidal air and in column 4 the tidal air at the end of a rebreathing experiment. The last we have called the "maximum tidal air" because it is the largest respiratory volume which the subject will exchange under the influence of the strongest respiratory stimulus that can be applied, carbon dioxid.

TABLE 2

Vital capacity and tidal air

NUMBER AND NAME	VITAL CAPACITY	CALCULATED VITAL CAPACITY LUNDSGAARD	RESTING TIDAL AIR	TIDAL AIR AT END OF REBREATHING	DIAGNOSIS AND REMARKS
1. D. P. B...	4537	3332*	580	2407	Normal
2. J. P.....	3953	3704	372	1929	Normal
3. T. deC....	3839			1249	Cardiac. Compensated
4. P. K.....	3503		371	1192	Gastric neurosis
5. A. J.....	2729		389	980	Shell shock. Effort syndrome
6. J. B.....	2519		737	1236	Cardiac. Slight dyspnea and hyperpnea
7. J. C.....	2432	2980	421		Cardiac. Compensated
8. J. A.....	2430	2930	439	1116	Cardiac. Compensated
9. C. D.....	2145		315	581	Cardiac. Severe decompensation
10. J. M. L...	1789		390	1309	Cardiac. No dyspnea nor hyperpnea
11. A. R.....	1789	3640	604		Nephritic. Mild acidosis
12. R. W.....	1714	3930	244		Cardiac. Some dyspnea
13. J. J. F....	1704		304		Cardio-nephritic. Mild acidosis
14. W. W.....	1452	4698	469		Cardiac. Some dyspnea
15. D. O. C...	1303	3540	423	638	Cardiac. Marked dyspnea
16. S. I.....	1248		375		Cardiac. Severe dyspnea
17. J. M.....	1197		475		Cardiac. Extreme cyanosis. Some dyspnea
18. Jos. C....	1182		385	492	Cardiac. Marked dyspnea

* See note, table 1.

Peabody (5) found the average resting tidal air slightly reduced in cardiac dyspnea. This our figures do not show. If such a reduction

exists it is small in proportion to the enormous reduction found in the vital capacity.

The maximum tidal air, on the other hand, varies almost directly with the vital capacity and the ratio between the two shows the same range of variation in cardiac patients with dyspnea as in normals (0.35 to 0.55). Number 10 is the only exception to this rule. In his case the "maximum tidal air" was very large in proportion to the vital capacity. It was noted in the course of the experiment on this patient that he could not be induced to exert himself to the full extent of his strength when he blew into the spirometer. The low vital capacity, in this instance, may be only an expression of lack of effort on the part of the patient. This was completely overcome under the stimulus of carbon dioxid and he showed a normal "maximum tidal air," although he did not continue rebreathing to the point of exhaustion.

In the case of the decompensated cardiac patients, however, there was no lack of effort apparent during the determination of the vital capacity. Moreover, two of them continued rebreathing to the point of extreme exhaustion. The reduction of the "maximum tidal air" and the vital capacity may be a functional matter, due to reflex inhibition. If so, this inhibition is so profound that it can not be overcome by the strongest stimulus which can be applied. The increase in the tidal air which normally occurs in response to the stimulus of carbon dioxid is limited by the lowered vital capacity.

DISCUSSION

Siebeck (1), in 1912, measured the lung volume in a series of cardiac patients by a rebreathing method. His studies showed that in cardiac dyspnea the residual air was relatively increased, although the absolute values he obtained seem to have been lower than normal. The reserve air and the complementary air were both decreased. These results are substantially the same as ours. However, Siebeck regarded them as questionable because he was unable to obtain the same constancy in his rebreathed mixtures in cardiac patients as in normals. In the latter the concentration of hydrogen in the rebreathing bag became constant after 5 respirations. In subjects with cardiac dyspnea the concentration continued to change even after 10 respirations. This Siebeck considered to be due to improper diffusion of air in the lungs. He concluded that the actual volume of residual air was greater than that indicated by the rebreathing methods.

As Sonne (6) has shown, the residual air can be measured with only an approximate degree of accuracy even in the normal person. Whether Siebeck is right in believing that the amount of air present is greater than that found, we are unwilling to argue. In two or three cases the number of respirations, the time and the volume of air rebreathed were varied without significant changes in the values obtained. This does not agree with Siebeck's findings. But any air that may be present and undetected must be peculiarly useless for respiratory purposes. A functional conception of the lungs is of more value than a purely anatomical one. In a normal person residual air determinations may be considered as measurements of the volume of air space in the fully deflated lungs, which is available for the rapid diffusion of gases. In this sense, certainly, the residual air is not increased in cardiac dyspnea. Since the vital capacity is decreased the effective volume of the lungs must be diminished.

Whether this diminution is due to a true anatomical lesion or not, we are unprepared to say. In some instances hydrothorax plays a part, but it is by no means an essential part. This we may assume not only because of the absence of physical signs of fluid, but also because of the rapidity with which the vital capacity increases as compensation is established (7).

Just what effect such a diminution of the lung volume may have on the gas exchange must be largely a matter of speculation until the cause of the diminution is determined. If it is not due to a true anatomical lesion it is quite possible that some or all of the blood in the pulmonary vessels is not in gaseous equilibrium with the alveolar air. This might, in part at least, explain the discrepancy between the alveolar CO_2 and the CO_2-combining capacity of the plasma.

This discrepancy Pearce (8) has attributed entirely to the effect of stasis in the general circulation. He has drawn a fine distinction between the causes of the low alveolar CO_2-tension in congenital heart disease, pneumonia and acquired heart disease. In congenital heart disease part of the venous blood does not pass through the lungs, and in consequence is given no opportunity to rid itself of the CO_2 which it has received from the tissues. In consequence the arterial blood is a mixture of aërated and unaërated blood. If there were no compensatory reaction a true carbon dioxid acidosis would occur. The respiratory mechanism, however, responds to the stimulus of the carbon dioxid. The alveolar CO_2-tension and the CO_2-tension of the blood which does pass through the pulmonary circulation is reduced suffi-

ciently to restore the CO_2-tension and hydrogen-ion concentration of the arterial blood to normal.

In patients with pneumonia in whom Pearce found the same discrepancy between the alveolar CO_2-tension and the plasma bicarbonates, he advances a similar explanation. In this case, although all the blood passes through the pulmonary circulation, he supposes that part of the blood passes through non-aërated portions of the lungs. On what seems to us insufficient evidence, he denies the possibility of such a condition in acquired cardiac disease. But certainly the reduction of the effective lung volume renders it not only possible, but not improbable. Even if Siebeck is right and this diminution is not due to a decrease in the actual air-containing space in the lungs, a certain part of this air must be unavailable for the rapid diffusion of gases and that portion of blood in the pulmonary circulation which comes in contact with this air must be less effectively ventilated than normal.

That the blood flow is retarded in decompensated cardiac disease is probable in the light of Harrop's (9) observation of an increase in the difference of the oxygen content of arterial and venous blood.

That this is the sole factor in the production of the low alveolar CO_2 remains to be proved. It is doubtful whether the method of Christiansen, Douglas and Haldane (10), which was employed by Pearce for the determination of the rate of blood flow, can be interpreted quantitatively in cardiac dyspnea. In this method it is assumed that the CO_2-tension of the alveolar air is the same as that of the arterial blood. That such a relation obtains in cardiac dyspnea demands definite proof. The use of respiratory methods that are designed to determine the venous CO_2-tension is also open to question when applied to conditions in which the venous oxygen unsaturation is excessive. Christiansen, Douglas and Haldane showed that the effect of oxygen on the carbon dioxid dissociation curve necessitated the introduction of a correction for the oxygen unsaturation even in normal persons. The extent of this correction in cardiacs can only be guessed.

Although the effect of the small effective lung volume on the exchange of gases between the blood and the alveolar air remains largely a matter of speculation, its effect on the mechanics of respiration is fairly clear. Here we have to deal only with the vital capacity, the portion of the lung volume available for ventilation of the lungs.

Apparently the reduction of vital capacity which occurs during cardiac dyspnea has little effect in limiting the respiratory exchange

during rest. The volume of the resting tidal air is not diminished. On the other hand, the amount by which the tidal air can increase under the stimulus of carbon dioxid seems to be distinctly limited by the reduction of the vital capacity. The reserve of the mechanical apparatus of respiration is therefore greatly diminished.

CONCLUSIONS

1. In cardiac patients with dyspnea no evidence of an increased residual air was obtained by the Lundsgaard method.

2. As the vital capacity is diminished, this means that the effective lung volume, the volume of air in the lungs available for the exchange of gases, is diminished.

3. The maximum volume of tidal air attained under the stimulus of continuous rebreathing is lower than normal in cardiac dyspnea. The reduction in the maximal tidal air bears a close relation to the reduction in vital capacity.

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STUDIES OF THE RESPIRATORY MECHANISM IN CARDIAC DYSPNEA

III. The Effective Ventilation in Cardiac Dyspnea

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In the previous papers of this series (1), (2) it has been shown that the effective lung volume is decreased during the dyspnea of cardiac decompensation. The alveolar CO_2 tension, as determined by the Haldane method, is usually low and always lower than the concentration of the bicarbonate in the venous plasma would indicate. We have shown that the air obtained by Haldane's method is probably true alveolar or exchange air. In this paper we shall present evidence to substantiate this contention and shall discuss the influence of a low alveolar CO_2 tension and of a diminished lung volume upon the effective ventilation in relation to the dyspnea of heart disease.

Peabody, Wentworth and Barker (3) find that, although the level of metabolism is normal or only moderately increased during cardiac decompensation, the minute volume of respiration is much greater than in normal individuals. The increase is accomplished by a more rapid respiratory rate with a moderate diminution in the volume of each expiration. The percentage of CO_2 in the expired air is diminished.

Peabody recognizes that the greater observed minute volume may represent no increase in the amount of effective air breathed. The tidal air consists of two parts. The dead space, which fills the upper respiratory tract is practically atmospheric air and is of no value in the ventilation of the functioning portions of the lungs. It is only the remainder of an expiration, the exchange air, which is effective for purposes of respiration. In any given expiration, the relative proportion of dead space to exchange air will determine the efficiency of ventilation. If, as Peabody assumes, the volume of the dead space is not changed during decompensation while the volume of tidal air

is diminished, the amount of effective air in each expiration will be diminished.

It is possible to arrive at a rough estimate of the effective minute volume by subtracting an average dead space value from the volume of the tidal air and multiplying the remainder by the respiratory rate. Different observers, Haldane and Priestley (4), Krogh and Lindhard (5) and Pearce (6), have found the volume of the dead space in normal resting subjects to vary between 100 and 200 cc. with an average of about 130 cc. Since there is no evidence that the dead space is changed in cardiac dyspnea and experiments reported in a previous paper (1) indicate that it cannot be greatly above the normal values, 130 cc. has been used as the average volume of the dead space for purposes of calculation.

To determine the effective ventilation, we made a considerable number of observations on the minute volume of normal individuals and of compensated and decompensated cardiacs. The method did not differ from that of Peabody except that a nose clip and rubber mouthpiece were substituted for the Siebe Gorman mask. The instrumental dead space was 30 cc. The expiratory air was collected in an accurately balanced Tissot spirometer for periods varying from five to ten minutes, the volume of expiration and the number of respirations being recorded for each minute. Volumes were reduced to standard conditions of 760 mm. Hg. and 0°C. To these observations we applied the following formula:

(Tidal Air − 160[1]) Respiratory Rate = Effective Minute Volume

The results are tabulated in table 1.

For the purpose of comparing our results with those of Peabody we have calculated the effective minute volume from his figures. The dead space of the Siebe Gorman mask which he used has been estimated at about 50 cc. Averages of the results are given in table 2.

The results of the two experiments are in practical agreement. In the decompensated cases, the minute volume of respiration is greater and the respiratory rate is increased. The volume of the tidal air is sometimes slightly diminished but this is by no means invariable as is shown by the large tidal air of J. B. and J. D. B. (table 1). The effective minute volume is much greater during decompensation.

It might be argued that the increase in effective ventilation is due to the higher level of metabolism and the consequent increase in CO_2

[1] To the average dead space of the individual has been added the instrumental dead space of 30 cc.

production which is observed in many dyspneic cardiac patients. That this is not true can be demonstrated by calculations from Peabody's figures (table 3).

Figures for surface area show that the average size of the patients in the two groups is practically identical. Differences either in the production of CO_2 or in the effective ventilation cannot be due to discrepancies in size. The CO_2 production per minute is only 5.1 per cent greater in the decompensated cases. The volume of effective air breathed per minute is 30.3 per cent higher than in the cases without

TABLE 1

SUBJECT	MINUTE VOLUME	TIDAL AIR	RESPIRATIONS PER MINUTE	EFFECTIVE MINUTE VOLUME	DIAGNOSIS AND REMARKS
	cc.	cc.			
D. P. B.	6,900	532	13.0	4,822	Normal adult
	6,789	580	11.7	4,913	
	6,040	592	10.2	4,406	
	6,751	668	10.1	5,131	
J. P.	5,524	372	14.9	3,148	Normal adult
	4,898	389	12.6	2,885	
	7,127	520	13.7	4,943	
G. C. D.	6,386	484	13.2	4,277	Normal adult
	6,243	488	12.8	4,198	
P. K.	4,659	293	15.9	2,115	Gastric neurosis. No sign of cardiac or pulmonary disease
	7,764	371	20.9	4,420	
Cap.	7,866	333	23.6	4,083	Normal adult. Respirations rapid and variable. Obviously over-ventilating
J. A.	6,474	439	14.8	4,106	Chronic cardiac valvular disease. No dyspnea while at rest in bed
	7,611	408	18.6	4,626	
J. M. L.	4,553	390	11.6	2,675	Chronic cardiac valvular disease. No dyspnea while at rest in bed
	6,133	438	14.0	3,893	
R. W.	5,826	244	23.9	2,003	Chronic cardiac valvular disease. Breathing quietly while at rest in bed. Rapid and superficial during experiment
J. W.	7,680	410	18.7	4,675	Chronic nephritis. Hypertension. No dyspnea while at rest in bed
Average	6,401	442	15.2	3,973	

TABLE 1—*Concluded*

SUBJECT	MINUTE VOLUME	TIDAL AIR	RESPIRATIONS PER MINUTE	EFFECTIVE MINUTE VOLUME	DIAGNOSIS AND REMARKS
	cc.	*cc.*			
J. B.	13,170	737	17.9	10,310	Chronic cardiac valvular disease. Dyspnea and cyanosis while at rest
	10,210	612	16.7	7,540	
Jos. C.	13,590	385	35.3	7,936	Chronic nephritis with hypertension. Severe cardiac decompensation with marked dyspnea
	14,140	350	40.3	7,638	
C. D.	9,982	315	31.8	4,916	Chronic cardiac valvular disease. Severe dyspnea and orthopnea
S. I.	6,930	375	18.5	3,970	Chronic cardiac valvular disease. Massive hydrothorax. Dyspnea and orthopnea
D. O. C.	8,069	423	19.1	5,020	Chronic cardiac valvular disease. Marked cyanosis and moderate dyspnea while at rest. Right hydrothorax
W. W.	9,528	469	20.3	6,279	Chronic cardiac valvular disease. Moderate dyspnea while at rest
J. R.	11,393	311	36.7	5,542	Chronic cardiac valvular disease. Marked dyspnea and orthopnea while at rest
	10,110	357	28.3	5,575	
P. O. S.	9,087	279	32.6	3,879	Chronic cardiac valvular disease. Right hydrothorax. Marked dyspnea and orthopnea while at rest
J. D. B.	14,310	821	17.4	11,501	Chronic cardiac valvular disease. Marked dyspnea and orthopnea while at rest
	12,800	538	23.8	8,996	
J. M.	8,652	475	18.2	5,733	Chronic cardiac valvular disease. Extreme cyanosis and some dyspnea while at rest
	9,843	496	19.8	6,653	
Average	10,788	463	25.1	6,766	

dyspnea. Only a small part of the increase in effective ventilation can be accounted for by a greater CO_2 production.

Furthermore, since the dyspneic cardiac breathes a much greater amount of CO_2, each volume of his effective or alveolar air must contain a smaller percentage of CO_2.

TABLE 2

	COMPENSATED CARDIACS	DECOMPENSATED CARDIACS
Minute volume (cc.*)	5,901	8,521
Tidal air (cc.)	460	398
Respiratory rate	13.2	21.8
Effective minute volume (cc.)	3,530	4,600

* Minute volumes have been recalculated from the CO_2 produced per minute and the percentage of CO_2 in the expired air.

TABLE 3

	COMPENSATED CARDIACS	DECOMPENSATED CARDIACS
Surface area (square meters)	1.72	1.77
CO_2 production per minute (cc.)	196	206
Effective minute volume (cc.)	3,530	4,600

It is possible to show more directly the probability of a reduced alveolar CO_2 tension. In the paper describing their method of obtaining alveolar air, Haldane and Priestley (4) indicated a means of determining the volume of the dead space. The data necessary for the calculation were the volume of an expiration, the percentage of CO_2 in the expired air and the percentage of CO_2 in the alveolar air. These were combined in the following formula:

Formula I

$$\text{Tidal air} - \frac{\text{Tidal air} \times \text{per cent } CO_2 \text{ in expired air}}{\text{Per cent } CO_2 \text{ in alveolar air}} = \text{Dead space}$$

By a simple inversion of their formula, the percentage of CO_2 in the alveolar air can be deduced.

Formula II

$$\frac{\text{Tidal air} \times \text{per cent } CO_2 \text{ in expired air}}{\text{Tidal air} - \text{Dead space}} = \text{Per cent } CO_2 \text{ in alveolar air}$$

Both of these formulae were applied to observations on a number of normal individuals and on cardiacs in varying degrees of decompensation. Minute volume determinations were made as in the previous experiments. At the close of an observation, the air was thoroughly mixed in the spirometer and a sample was taken for analysis. Haldane

TABLE 4

SUBJECT	MINUTE VOLUME	RESPIRATIONS PER MINUTE	TIDAL AIR	CO_2 IN EXPIRED AIR	ALVEOLAR CO_2 CALCULATED FROM DEAD SPACE FORMULA	ALVEOLAR CO_2 OBSERVED HALDANE METHOD	ALVEOLAR CO_2 CALCULATED FROM PLASMA BICARBONATE	DEAD SPACE CALCULATED FROM		DIAGNOSIS AND REMARKS
								Observed alveolar CO_2	Alveolar CO_2 calculated from plasma	
	cc.		*cc.*	*per cent*	*per cent*	*per cent*	*per cent*	*cc.*	*cc.*	
D. P. B.	6,040	10.2	592	3.92	5.39	5.39		130		Normal adult
	6,751	10.1	668	4.16	5.47	5.40		123		
J. P.	4,898	12.6	389	3.84	6.52	5.89		105		Normal adult
	7,127	13.7	520	4.29	6.14	5.75		132		
Cap.	7,866	23.6	333	3.27	6.29	6.31		130		Normal adult
G. C. D.	6,386	13.2	484	3.42	5.11	6.39		195		Normal adult
	6,248	12.8	488	4.04	6.01	6.63		161		
J. W.	7,680	18.7	410	3.03	4.98	4.85	5.60	124	158	Chronic cardiac valvular disease. No dyspnea while at rest
Average	6,625	14.4	486	3.75	5.74	5.83		138		
J. R.	11,396	36.7	311	2.16	4.44	4.60	6.73	139	181	Chronic cardiac valvular disease. Dyspnea and orthopnea while at rest
	10,110	28.3	357	2.33	4.26	3.95		115		
J. D. B.	14,310	17.4	821	2.14	2.66	3.11	5.53	226	473	Chronic cardiac valvular disease. Moderate dyspnea and cyanosis
	12,800	23.8	538	2.69	3.82	4.53		189		
J. M.	8,652	18.2	475	2.40	3.62	3.39	5.76	109	247	Chronic cardiac valvular disease. Extreme cyanosis, moderate dyspnea
	9,843	19.8	496	2.72	4.02	4.96	7.41	195	284	
P. O. S.	9,087	32.6	279	2.30	5.39	5.69	7.40	136	162	Chronic cardiac valvular disease. Severe decompensation with dyspnea and orthopnea
Average	10,885	25.2	469	2.39	4.03	4.32		159		

samples of alveolar air were taken before and after the minute volume determinations. A specimen of blood was drawn from an arm vein for determination of the bicarbonates in the plasma. The results obtained from the plasma were converted into terms of percentage of alveolar CO_2 according to the method of Van Slyke (7).

In formula II, average dead space values were employed for the calculation of the probable percentage of CO_2 in alveolar air. The results are recorded in table 4 (column 6). They agree closely with the results of direct observation by the Haldane method (column 7) and consequently in the decompensated cardiac lie far below the value indicated by the plasma (column 8).

In formula I, the observed alveolar CO_2 per cent and the percentage indicated by the plasma have been applied to calculate the probable dead space. Substitution of the observed values give volumes of dead space which are within the range of normal (column 9) while substitution of percentages indicated by the plasma give decidedly improbable results (column 10).

Formula II has also been applied to Peabody's figures. Averages are given in table 5.

TABLE 5

	COMPENSATED CARDIACS	DECOMPENSATED CARDIACS
Tidal air (cc.)	466	398
CO_2 in expired air (per cent)	3.35	2.44
Calculated alveolar CO_2 per cent (using dead space of 180 cc.)*	5.72	4.70

* Average dead space of 130 cc. to which is added the extra dead space of 50 cc., the capacity of the Siebe Gorman mask.

Both in Peabody's figures and in ours, the percentage of CO_2 in the alveolar air is lower during decompensation.

DISCUSSION

In this series of papers the question of the concentration of CO_2 in alveolar air during cardiac decompensation has been approached from several angles. Of the direct methods, that of Haldane which has been found applicable to dyspneic patients gives values for alveolar CO_2 percentage much lower than it does in normal individuals. Duplicate samples, however, show quite as close agreement in dyspneic

cardiacs as in trained normal subjects. Experiments have shown that the low content is not due to subjective errors nor to an increased dead space. After breathing increasing percentages of CO_2, the alveolar CO_2 percentage of dyspneic cardiacs is still relatively lower than it is in normal individuals under the same circumstances. The percentage, moreover, is not increased by increasing the depth of expiration. An expiration of maximum depth contains no greater concentration of CO_2 than does one of a volume just sufficient to clear the dead space. Whether the specimen of air obtained by the Haldane method is from the alveoli or from other portions of the lungs is not of great importance in the present discussion. Whatever the anatomical source of the sample may be, it is the only air which by the greatest effort the decompensated cardiac can expire. It is the only air which can be functionally effective in the elimination of CO_2 from the body. If this is true the CO_2 contained in this air should completely account for the total CO_2 elimination. In this paper it has been shown by the use of Haldane's dead space formula that the percentage of CO_2 found in the Haldane specimen is the percentage theoretically required to account for the CO_2 eliminated.

The accumulated evidence, both direct and circumstantial, indicates that the percentage of CO_2 is low in the effective air of dyspneic cardiac subjects. The cause of this important phenomenon is not clearly understood. Its chief importance in the present discussion lies in its effect upon the ventilation in cardiac disease.

A low percentage of CO_2 in the effective air necessitates a larger effective ventilation to accomplish CO_2 elimination. Even when the metabolism is normal, the decompensated cardiac exhibits hyperpnea. As long as he lies quietly in bed, this usually involves an increase in the rate of respiration with little or no change in the volume of each respiration. Under these circumstances the low effective lung volume, which is the constant accompaniment of decompensation, is not a factor of great importance in the causation of dyspnea. It probably exerts a greater influence during conditions involving a greater production of CO_2.

Concerning the mechanism of ventilation during exercise, we have accumulated no direct evidence. A good indication of the response is furnished, however, by experiments upon the rebreathing of CO_2. Under these circumstances the cardiac is subjected to a most powerful stimulus to respiration. The mechanism should, by analogy, be similar to that occurring during exercise or any other condition involving a

rapid production of CO_2 within the body. It has been shown that the cardiac maintains a relatively low alveolar CO_2 percentage during rebreathing. To accomplish this he must breathe a larger volume of effective air. Under the stimulus of CO_2, the volume of the tidal air increases both in cardiacs and in normal individuals. The increase, however, is in proportion to the vital capacity. In both groups the tidal air reaches a maximum at one-third to one-half of the volume of the vital capacity. Thus, a normal individual with an original vital capacity of 4000 cc. may show under the stimulus of CO_2 a tidal air of 1500 to 2000 cc. In a decompensated cardiac whose vital capacity may be only 1500 cc. the tidal air will not rise above 500 to 750 cc. with maximum CO_2 stimulation. The volume of respiration is strictly limited. Any attempt to increase it is accompanied by marked subjective dyspnea.

Two factors in cardiac disease help to explain the dyspnea which is its most constant subjective symptom. The low percentage of CO_2 in the effective air makes an increase in ventilation essential. The diminished effective lung volume makes any large increase difficult or impossible. The first is active under all conditions while the cardiac is decompensated. The second exerts its chief influence when the production of CO_2 in the body is increased.

CONCLUSIONS

1. Air obtained from decompensated cardiacs by the Haldane alveolar method is true exchange air. It corresponds to the alveolar air obtained by the same method in normal resting subjects. It is the only air effective for the elimination of CO_2.
2. During cardiac dyspnea, the bicarbonate content of the plasma gives no indication of the percentage of CO_2 in the exchange air.
3. The minute volume of effective or exchange air is increased during cardiac decompensation.
4. This is not explained by the higher level of metabolism.
5. The greater effective ventilation is necessitated by the low concentration of CO_2 in the exchange air.
6. Great increases in ventilation are impossible because of the diminished effective lung volume of decompensated cardiacs.

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STUDIES ON THE BRAIN STEM

IV. On the Relation of the Cerebral Hemispheres and Thalamus to Arterial Blood Pressure

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In a previous report (1) attention has been directed to the poikilothermous condition that follows the removal of the cerebral hemispheres and thalamus in birds and mammals. In an attempt to discover the causes of this condition it was suggested that possibly a general fall of arterial blood pressure with resulting cutaneous dilatation of the blood vessels might be an essential factor. To test this point a method was devised for measuring the arterial pressure in the pigeon and studies of the blood pressure made before and after reduction to the cold-blooded condition. These tests did not give the anticipated results but led to the discovery that the removal of the cerebral hemispheres, which alone does not reduce the bird to the cold-blooded condition, leads to a permanent slight fall in arterial tension. The plan of the work was therefore extended to a study of the arterial pressure in the normal pigeon, the normal variations, effects of various procedures on the normal pressure, and then, the effect of various types of brain lesions on the arterial pressure.

Asher (2) in his review of the vasomotor mechanism, in 1902 wrote: "There are no known facts which indicate the presence of vasomotor centers in the parts of the brain above the medulla oblongata. The higher cerebral centers influence the vasomotor tone exclusively in a reflex manner through the medullary vasomotor center." This interpretation is based on the original experiments of Ludwig's students, Dittmar and Owsjannikow. These classic experiments in 1872 and 1873 demonstrated the localization of the vasoconstrictor centers in the floor of the fourth ventricle.

Since then innumerable studies have demonstrated that reflex influences from the cerebral hemispheres above and the spinal nerves below

may play on this center. (Literature cited by Sachs.) It has become common knowledge that loss of the cerebral hemispheres does not necessarily disturb the arterial pressure in acute experiments. It therefore came somewhat as a surprise to find that in a series of decerebrate birds, kept for several weeks or months after removal of the cerebrum, the arterial pressure was uniformly lower than in normal birds.

Porter showed in 1907 that in curarized rabbits and cats removal of the cerebral hemispheres in acute experiments leads to a profound fall in the blood pressure without depression of the reflex excitability of the vasomotor center.

If a blood pressure tracing be made on a dog before and after decerebration by Sherrington's method, it is frequently found that the pressure is somewhat less after decerebration than before. The complications however of the muscular rigidity that follows, render difficult the interpretation of the effects of the operation on the vasomotor center.

All these experiments are acute traumatic experiments subject to all the uncertainties of shock effects. In the birds many of these difficulties can be obviated, for they can be kept alive easily, for an indefinite time after the operation, and spastic paralytic phenomena are wholly lacking provided the hemispheres only are removed. In the pigeon therefore we have a warm-blooded animal which easily withstands the shock of cerebral ablation, lives indefinitely thereafter, and in which the permanent effects on the blood pressure can be studied.

There was the further inducement that the pigeon in comparison with the mammals combines a relatively low type of cerebral development with the warm-blooded condition and it was hoped that some light would be thrown on the nature of the nervous mechanism of heat regulation in its earlier development.

Methods. The measurements of arterial pressure were at first made in the ordinary way of cannula and mercury manometer. It was soon found that a more convenient and just as reliable method was furnished by substituting a hypodermic needle for the cannula and this method was used in all the work here reported. All measurements have been made on the brachial artery using a hypodermic needle, size 19 or 20 with a bore of about 1 mm. diameter. This furnishes a tube which when inserted into the artery slightly stretches it and fits tightly enough to allow no escape of blood. (In very large birds it may be necessary to use a larger needle.) This was connected to an ordinary small size mercury manometer made of glass tubing 4 mm. in diameter, with stiff-walled rubber tubing. In order to avoid any errors due to possible

mechanical effects of friction or differences in level between the bird and the level of the mercury, the manometer was set in a fixed position with the level of the mercury in the plane of the tip of the breast muscles when the bird was fastened on its back. The same manometer, two needles of the same size, and the same size and length of rubber connections, were used throughout the series. Hence any mechanical errors will be nearly uniform throughout the comparative series of pressure determinations. Clotting of the blood was prevented by using 7 per cent sodium citrate throughout the apparatus. A lesser concentration was not always satisfactory, but with citrate solution of this concentration the tracing can be continued indefinitely through all variations of blood pressure of zero to 200 mm. When the needle was removed from the artery the blood vessel was doubly ligated. This causes no apparent trouble to the bird, so the collateral circulation must be extensive. In only one case did gangrene follow the ligation and in this case the ligature involved both brachial artery and vein. All readings were made with the birds under ether anesthesia; no other drugs were used in this study. This introduced, of course, the effects of the anesthetic added to that of the cerebral lesion. No other method however seemed available for it is important that there be no struggles by the animal as these will promptly change the level of the arterial pressure. In order to check these variations due to the action of the anesthetic the routine procedure was adopted of etherizing the bird, putting it on its back with wings spread and the needle inserted in the artery. The pressure was then raised in the manometer to a value a little less than the anticipated pressure. Some care was necessary here not to exceed the arterial pressure and thereby kill the bird by forcing citrate into the circulation. This happened twice in the series of experiments. The arterial pressure was then recorded for all depths of anesthesia, varying from light to deep, using rigidity as an index of light, and abolition of the corneal reflex as index of deep anesthesia. The readings of pressure given in the tables are, therefore, those of the extreme variations under anesthesia, but not including variations due to struggles of the animal. In many cases the pressure maintained a nearly constant level and only one figure is given in such cases.

In order to determine whether or not there were errors due to possible differences in size of the arteries of the two wings, readings were made on a series of birds comparing specifically the pressures in each of the two brachial arteries, in the same bird, allowing intervals of several days between determinations, during which time the birds

were kept confined in the cages used throughout the series of experiments. These readings (table 5) agree closely. Of course in the case of specific anatomical anomalies such a comparison would be of no value. One such case has been seen, namely, a double instead of a single brachial artery. In a series of determinations however this

TABLE 1

Arterial pressure in normal pigeons

Anesthesia variations

NUMBER OF PIGEON	ARTERIAL PRESSURE	NUMBER OF PIGEON	ARTERIAL PRESSURE
	mm.		*mm*
4	122–142	190	104–114
	114–118	188	94–120
	116–118	158	110–130
	150–160	156	154–176
	122–132	178	92–140
153	108–142	161	78–130
170	136	163	108–116
172	103–118	162	106–108
171	135	179	122–160
	116	169	100–110
177	96–108	193	96–98
181	92–108	193	96–102
	126–152	194	122–140
185	116	194	106–124
164	134–176	195	110–148
182	92–118	195	104–128
184	88–128	159	150–170
183	86–112		104–120
186	102–118	168	122–144
187	90–110		

Average pressure, 118 mm.

Average limits of variations, 109–130 mm.

The figure 109 is the average of all the lower of the two readings given for the majority of the animals. Similarly 130 is the average of the higher reading given. The figure 118 is the average of these extremes combined with the single figure given for several birds.

factor is neutralized in the averages given, and by the consideration that the arteries of both wings were used indiscriminately throughout the series of determinations.

Normal blood pressure. The average arterial blood pressure in the brachial artery under ether anesthesia of thirty-nine normal adult pigeons was found to be 118 mm. (table 1). The extreme limits for

all stages of anesthesia were 78 to 176 mm. The average limits for the series are 109 to 130 mm. (fig. 1).

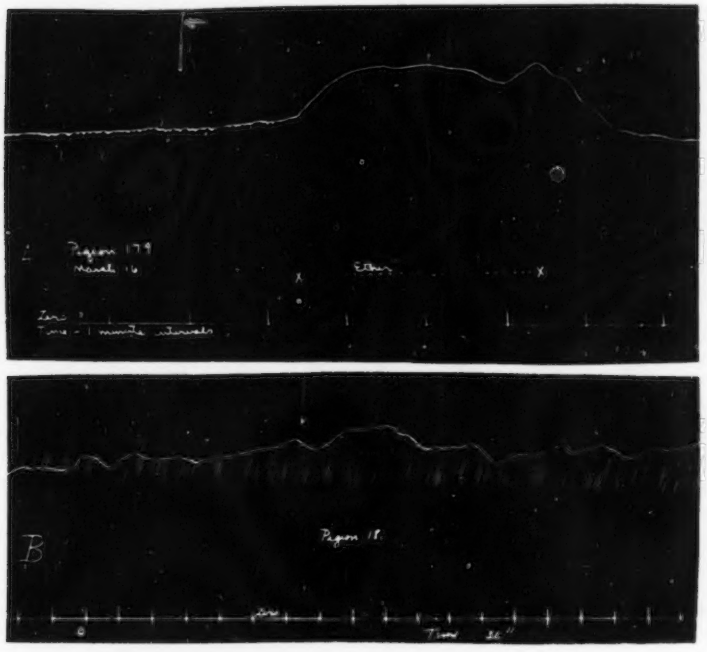

Fig. 1. Arterial pressure in normal pigeons, ether anesthesia. *A:* Light anesthesia: *x–x* more ether given so as to put bird in a state of deep anesthesia. Time in one minute intervals. *B:* Traube-Hering waves in pigeon under light anesthesia. Time in 30 second intervals.

Note: All figures of blood pressure are reduced one-half, except figure 3, which is reduced one-third. A true scale for measuring pressure in these tracings is given in figure 4.

Mechanical stimulation of the brachial nerves, ammonia to the nostrils, and asphyxia, produced the usual types of vasomotor responses. The effects of these procedures are given in table 2 and figures 2 and 3. Electric stimulation of these nerves was not employed. Mechanical stimulation of the nerves by pinching with forceps or traction caused brisk changes in arterial pressure, both pressor and depressor effects.

A lowering of blood pressure by cardiac inhibition seemed particularly easily elicited by traction of the brachial nerves. Traube-Hering waves of pressure have been frequently observed as also have been the shorter respiratory waves (fig. 1, B).

TABLE 2

Variations of arterial pressure in normal pigeons

NUMBER OF PIGEON	AVERAGE NORMAL PRESSURE	RANGE OF VARIATIONS OF PRESSURE INDUCED BY		
		Mechanical stimulation brachial nerves*	Ammonia to nostrils (rise in pressure)	Asphyxia (increased pressure)
	mm.	*mm.*	*mm.*	*mm.*
	110	14		24
	130		34	
	110		40	
153	125	30		
158	120	50	16	24
169	105	22	22	
178	116	12		
179	140	8	26	22
156	164	16	16	
170	110		32	

* This includes both pressor and depressor effects.

TABLE 3

Effects of slight hemorrhage on arterial pressure

NUMBER OF PIGEON	AMOUNT OF BLOOD LOST	ARTERIAL PRESSURE	
		Before bleeding	10 minutes after bleeding
	cc.		
159	5	150–170	126–128
173	1	110	102–118
155	2	130–150	134–148

The removal of small amounts of blood leads to a fall followed by quick recovery (table 3). Thus the loss of 1 to 2 cc. of blood in the normal pigeon leads to a fall quickly followed by compensatory changes which bring the pressure back to normal. The loss of 5 cc. of blood causes much more profound effects but in ten minutes the blood pressure has again reached the average level although below the previous level in the same bird (pigeon 159, table 3).

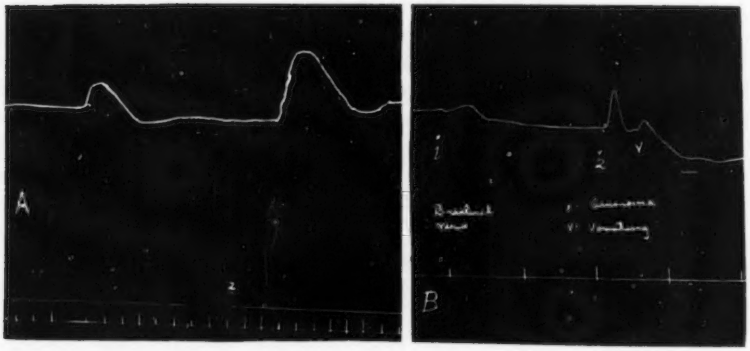

Fig. 2. Blood pressure, normal pigeons. *A: 1*, mechanical stimulation of brachial nerves; *2*, ammonia vapors to nostrils. *B:* Deeper anesthesia than in *A*. *1*, mechanical stimulation of brachial nerves; *2*, ammonia to nostrils; *V*, vomiting.

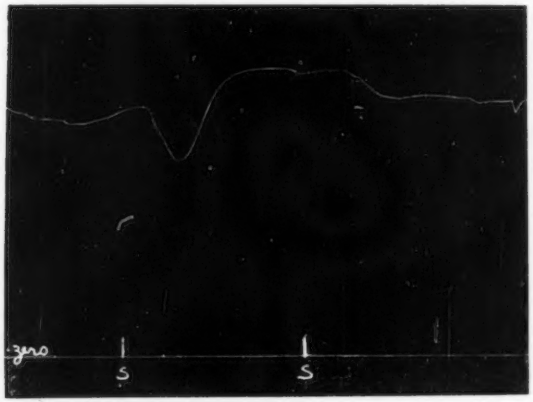

Fig. 3. Blood pressure, normal pigeon. Depressor effects following mechanical stimulation of brachial nerves.

The effect on blood pressure of deprivation of food—but not water—was tested on four birds. These birds were starved for four to eight days. At the end of that time the arterial pressure was normal in three of the birds and slightly lowered in one of them (table 4). The effects of confinement were tested by comparing the pressures of three birds which had been in the laboratory cages for over a year. The average pressure of these birds (six determinations, table 5) was 115 mm. compared with the average pressure of 118 mm.

TABLE 4

Influence of starvation on arterial pressure. Cerebrum intact

NUMBER OF PIGEON	STARVATION PERIOD	ARTERIAL PRESSURE	
		Before starvation	After starvation
	days	*mm.*	*mm.*
183	7	88–112	80–86
184	7	104–114	120–122
182	8	90–108	95–98
164	4	116–135	120–126

TABLE 5

Comparative pressure determinations in the two brachial arteries of the same birds (birds have been in laboratory cages for one year)

NUMBER OF PIGEON	TIME BETWEEN MEASUREMENT	RIGHT WING	LEFT WING
	days	*mm.*	*mm.*
193	3	96–98	96–103
194	3	122–140	106–124
195	3	104–128	110–148

Average pressure in these birds, 115 mm.

By this series of determinations of arterial pressure on thirty-nine normal adult pigeons the average pressure has been determined, the normal variations noted, and the effects of such factors as anesthesia, starvation and the routine reflexes observed. Preliminary to the production of cerebral lesions it was important to note whether or not the loss of the small amount of blood necessary to the operation would alter the level of the arterial pressure. As noted in table 3, the loss of 2 cc. of blood is so quickly compensated for as to justify the conclusion that if in operating not more than 2 cc. is lost the normal level of arterial pressure is maintained.

Effects of decerebration. A description of the varying conditions that follow the removal of the hemispheres or hemispheres and thalamus, or partial lesions of both, has been given elsewhere (7). It will suffice here to state that the classic picture of decerebrate behavior in the pigeon is obtained only if the thalamus be not traumatised in the process of decerebrating (8), (9). Thalamic injury is associated with temperature disturbances, with the behavior of the animal varying as its body temperature changes. The technique of decerebration is therefore important in a comparative series of studies on the rôle of these two parts of the brain. The general anatomy of this region of the brain is described in a previous paper (1). In decerebrating the upper part of the skull above the cerebral hemispheres was removed taking care not to puncture the dura mater. After a little practice this is easily done. A bridge of bone over the very small longitudinal sinus was left intact so as to diminish bleeding and to serve as a support for the skin after removal of the brain substance. The dura was then cut longitudinally and reflected, the anterior cerebral arteries were cauterized and the hemispheres removed in toto. In this way the operation can be completed with the loss of less than 1 cc. of blood. If more than 2 cc. of blood was lost in operating it is indicated in the history of the animals. If the thalamus was to be destroyed, this was done with an electro-cautery, after removal of the hemispheres. The autopsy findings in the brain with histologic description of the parts of the brain remaining after recovery from this type of injury have been described in the preceding report to which reference has been made (7).

It is common knowledge that the removal of the hemispheres sometimes leads to a slight immediate fall in blood pressure which has been attributed to shock, hemorrhage, mechanical stimulation, etc. The same effect is true of the pigeon. In order to avoid these acute effects, the birds have been kept for time intervals of one week to four months after decerebration before the arterial pressure was measured (table 6 and fig. 4). These studies have been carried out on fifteen pigeons, allowing time intervals for recovery from any acute shock effects. In ten of these birds the arterial pressure was measured before decerebration; in five this was not done. For the latter animals some indication of the change in pressure may be gathered by comparing with the average normal arterial pressure value given above.

The average pressure after decerebration, thalamus being left intact, allowing three to seventy-five days for recovery, in fifteen pigeons, was

found to be 99 mm., in comparison with the average pressure in thirty-nine normal pigeons, of 118 mm. This reduction seems to be uniform and constant, and continues for months after loss of the hemispheres. It is not due to loss of blood at the time of decerebration for the amount of blood lost was so slight that compensation quickly occurs in the normal animal. It is not due to failure of compensation in the decere-

TABLE 6

Effects on arterial pressure of removing the cerebral hemispheres, thalamus not traumatised

NUMBER OF PIGEON	TIME FOR RECOVERY*	ARTERIAL PRESSURE		REMARKS
		Before decerebration	After decerebration	
	days	*mm.*	*mm.*	
179	5	120	102	Much bleeding at time of operation
178	5	120–144	120	Good condition
156	5	154–176	96–112	Good condition
158	8	108–128	96–110	Good condition
168	16	118–124	92–120	Good condition
106	75		96–108	Good condition
155	3	126–136	96– 98	Good condition
166	16	120–122	104–114	Good condition
167	5	116–124	96–102	Good condition
152	16	82– 98	90– 95	Good condition
162	3	104–108	88– 94	Good condition
157	5		80– 84	Good condition
116	11		86– 90	Good condition
	21		96	Good condition
	6		87	Good condition

* The words "time for recovery" indicate the time interval elapsing between the removal of the cerebral hemispheres and the final blood pressure determinations. The words "good condition" indicate that the bird exhibited no skeletal muscle incoördination, body temperature was normal, feathers fluffed in the characteristic decerebrate manner and the bird exhibited decerebrate restlessness. Any variation from these characteristic effects usually indicate thalamic or medullary disturbances or incomplete decerebration.

brated bird, for when pressure tracings were made allowing the blood to force the mercury from the zero level, it rises to the level of arterial pressure as quickly in the operated birds as in the normal ones. (Compare figs. 5 and 8 A.) With decerebration plus thalamic lesions, slower compensation may be a factor (see below). This fall in pressure is not due to mere disturbances of food supply for, as tested in normal

birds (table 4), complete starvation for periods of three to eight days did not cause greater variations in pressure than the normal anesthesia variations. It might be due to one or more of the following factors.

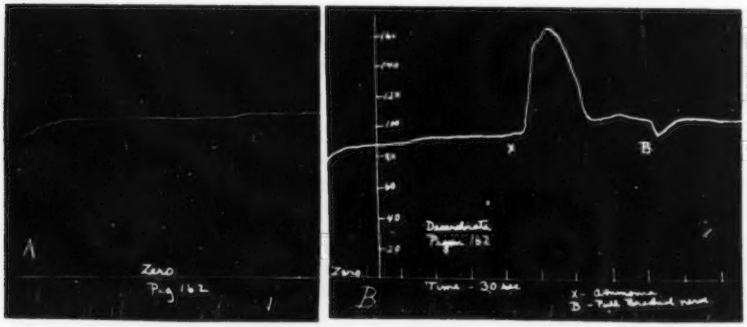

Fig. 4. Blood pressure, pigeon 162: *A:* before, and *B:* eight days after removal of the cerebral hemispheres. Thalamus intact and body temperature normal. Time in 30 second intervals. *B: x*, ammonia to nostrils; *b*, mechanical stimulation of brachial nerves.

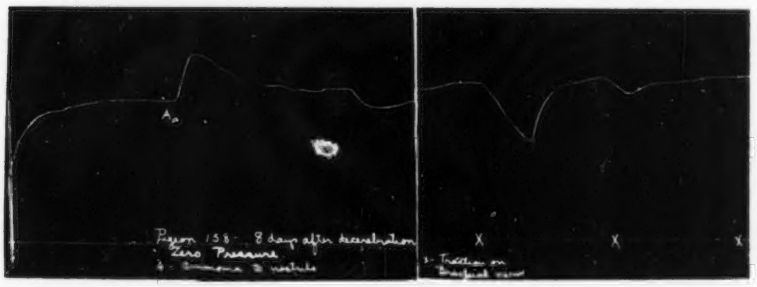

Fig. 5. Blood pressure, pigeon 158, eight days after decerebration. *A:* ammonia to nostrils; *X:* mechanical stimulation of brachial nerves, repeated three times. There was no preliminary increase in pressure in manometer before making this tracing, so the mercury was forced up from the zero line wholly by the arterial pressure.

First, metabolic depression following loss of the hemispheres associated with decreased activity of the animal; or second, loss of a tonic activity of the hemispheres on the vasoconstrictor centers; or possibly due to depressed skeletal muscle tone with resulting capillary dilatation.

In order to test the first of these possibilities the blood pressure determinations were made on a normal pigeon before and after blinding and starvation. Blinding the bird by excision of the eyes brings about a condition of quiet and lessened muscular activity that simulates that of decerebration. The combination of starvation for four days associated with this inactivity of blindness did not lower the average arterial pressure (see table 4, pigeon 164). Of course prolonged starvation for a long period of time will alter the pressure, witness pigeon 183, table 4, and pigeon 188, table 9. Inasmuch as all decerebrate birds were fed by hand and kept in as good condition as possible, it seemed that one week of absolute starvation would represent as great a metabolic disturbance as might be induced by loss of the hemispheres. The result of this test therefore suggested that the fall in arterial pressure is due to the loss of reflex or tonic influences from the cerebrum on some part of the blood pressure regulating mechanism.

In the decerebrate pigeon, thalamus not traumatised, the usual types of vasomotor reflexes may be elicited by stimulation of spinal nerves, ammonia, etc. (fig. 5). Asphyxia produces the usual rise in pressure.

Decerebration with destruction of the thalamus. Combined decerebration and thalamic cauterization abolishes the ability to maintain and regulate the normal body temperature of the pigeon (39° to 41°C.). As stated in the introduction, it was thought that possibly this condition might be due to a generalized fall in blood pressure. As is evident from table 8, this is not the case. If the body temperature of such a bird is kept near the normal level by keeping the bird in an incubator at 30°C. the arterial pressure of such a bird is very near the pressure of the warm-blooded decerebrate pigeon. Thus the average values of blood pressure, decerebrate pigeons (body temperature normal) and decerebrate-thalamic destruction (cold-blooded animals) are as follows:

TABLE 7

BIRDS	NUMBER OF BIRDS	BODY TEMPERATURE	ARTERIAL PRESSURE
		°C.	mm.
Normal	39	39–41	118
Decerebrate	14	39–41	99
Decerebration and thalamus destroyed	7	34–41	99
Decerebration and thalamus destroyed	7	26–33	87

It is conclusively evident from this table that the loss of temperature regulation is not due primarily to a lowered arterial pressure, but that the changes of arterial pressure are secondary to the body temperature changes. As the body temperature rises or falls the blood pressure does likewise (table 8 and fig. 6). To this rule one exception was found, pigeon 174. In this animal the pressure did not fall as the body temperature fell, but acted in an inverse manner. Attempts were made to duplicate this but were unsuccessful. This was a bird in which the operation of decerebration was associated with much bleeding. The writer is inclined to attribute the high arterial pressure in this bird to a possible intracranial pressure complication or incomplete destruction of the thalamus.

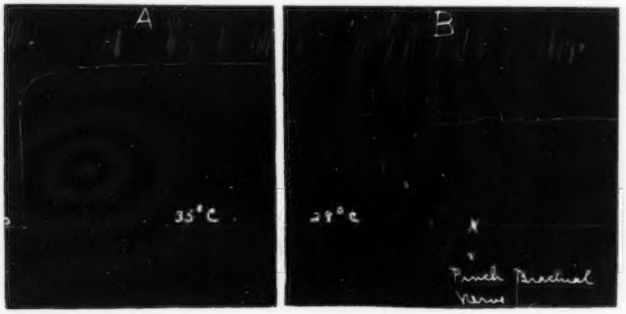

Fig. 6. Blood pressure in pigeon 191. Poikilothermous bird; decerebrate and thalamus destroyed. *A:* **Body temperature of pigeon, 35°C.** *B:* **Body temperature of pigeon, 28°C.** *x*, **mechanical stimulation of brachial nerves.**

In the poikilothermous pigeon the vasomotor reflexes vary in intensity as the body temperature varies (figs. 6 and 7). Both pressor and depressor effects were obtained by stimulation of the brachial nerves. As the body temperature falls the pressor reflexes particularly decrease in intensity. The depressor effects seemed to be due to cardiac inhibition and were present at low body temperatures at which the pressor effects were very much reduced (compare figs. 6 and 7). Ammonia to the nostrils caused a rise in pressure which is associated with respiratory distress. This effect was present at all body temperatures tested (28° to 41°C.), but was more sluggish at lower temperatures than at normal body temperature (compare figs. 5, 7 and 8).

TABLE 8

Arterial pressure in pigeons rendered poikilothermous by destruction of cerebrum and thalamus

NUMBER OF PIGEON	DATE	PROCEEDING	TIME FOR RECOVERY	BODY TEMPERATURE	ARTERIAL PRESSURE
			days	*°C.*	*mm.*
191	June 22	Operation		39	
	June 28	Blood pressure	6	35	93
	June 28	Blood pressure	6	28	58
175	March 9	Operation		39	
	March 14	Blood pressure			
		1 p.m.	5	36	102–106
		6 p.m.	5	28	83–86
174	March 5	Operation, much bleeding		40	
	March 10	Blood pressure			
		2 p.m.	5	34	121
		4 p.m.	5	31	124
		6 p.m.	5	29	124–134
114	February 7	Operation		39	
	February 22	Blood pressure	15	29	92
	March 8	Blood pressure	29	41	85
	March 13	Bird dead			
113	February 7	Operation		3	
	February 20	Blood pressure	13	28	92
		Operation	3	29	78
		Operation	29	41	85
176	March 9	Operation		39	
	March 12	Blood pressure	3	29	76
	March 13	Dead			
180	March 18	Operation, much bleeding		39	
	March 29	Blood pressure	11	34	102–106
169	March 1	Blood pressure tracing, followed by operation on brain		39	100–110
	March 4	Blood pressure	3	31	72–76

Body temperatures of the operated birds fixed by varying the temperatures of bird cages.

Average arterial pressure—body temperature 34–41°C.—was 99 mm.

Average arterial pressure—body temperature 28–31°C.—was 87 mm.

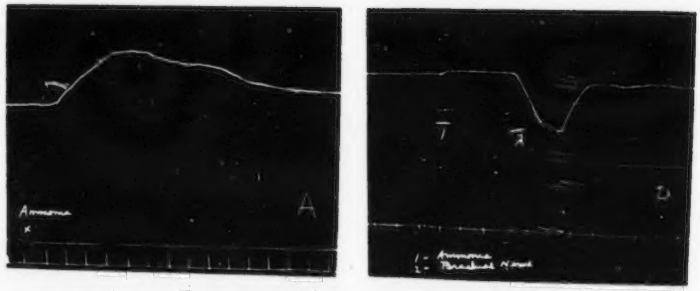

Fig. 7. Blood pressure, poikilothermous pigeons. *A:* Pigeon 169. Body temperature 31°C. Time in 15 second intervals; *x*, ammonia to nostrils. *B:* Pigeon 175. Body temperature 28°C. *1*, ammonia to nostrils; *2*, traction on brachial nerves.

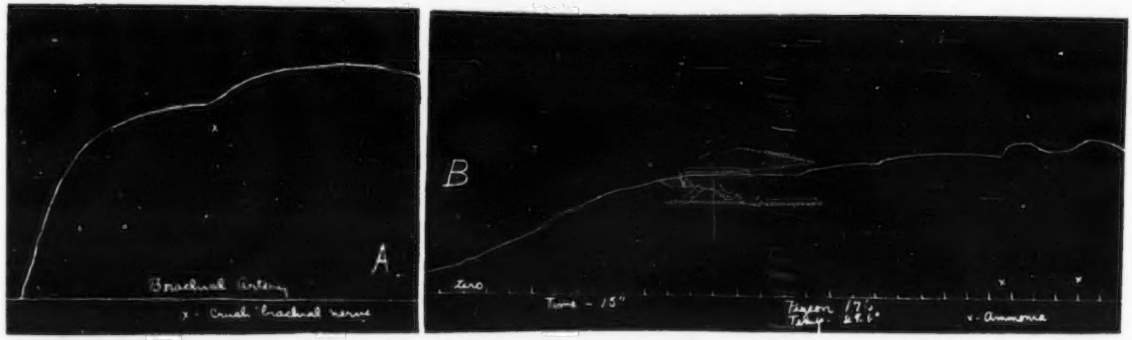

Fig. 8. Comparison of the time rates at which the pressure rises from the zero level of the manometer wholly under the influence of the arterial pressure. *A:* Normal pigeon, body temperature 39°C.; *x*, stimulation brachial nerves. *B:* Poiki othermous pigeon, body temperature 29°C.; *x*, ammonia to nostrils.

Compensation after loss of a small amount of blood occurs more and more slowly as the body temperature is more and more depressed (fig. 8). In this figure the pressure in the manometer was at zero when the artery was connected with it. The slow rise to the level of arterial pressure is in marked contrast to the quick ascent and maintenance of level in the normal bird.

Effects of localized lesions. The major part of the cerebral cortex had been destroyed by electro-cauterization in three birds a year previous to the determination of arterial pressure. All of these birds gave normal blood pressure values (table 10).

TABLE 9

Effects on arterial pressure of removing one cerebral hemisphere

NUMBER OF PIGEON	DATE	PROCEEDING	ARTERIAL PRESSURE	REMARKS
			mm.	
190	June 10	Blood pressure then operation	98–118	
	June 23	Blood pressure	96–122	Bird in good condition—eats and drinks
188	June 8	Blood pressure then operation	92–102	
	June 23	Blood pressure	80–96	Emaciated, does not eat
186	May 25	Blood pressure then operation	100–118	
	June 8	Blood pressure	108–120	Good condition, eats and drinks
187	May 25	Blood pressure then operation	94–110	
	June 7	Blood pressure	82–92	Poor condition, does not eat
	June 9	Bird dead of starvation		

In one pigeon both occipital poles of the cerebral hemispheres were removed and the dorso-median part of the thalamus cauterized without severing the forebrain bundles. Four months later the arterial pressure in this bird was normal (pigeon 118, table 10).

In one bird extensive cerebellar traumatism was done a year before the blood pressure determination. The bird regained its ability to coördinate its muscle activities in the usual way. Blood pressure

determination in this bird showed a lower arterial tension (pigeon 193, table 10). At autopsy the bird was found to be tubercular.

In a series of four birds the right cerebral hemisphere only was removed (table 9). After this operation some birds promptly recover and in a few days feed themselves in a normal way. The principal

TABLE 10

Arterial pressure after minor brain lesions

NUMBER OF PIGEON	DATE	OPERATION	ARTERIAL PRESSURE	REMARKS
			mm.	
118	April 28	Occipital cortex removed; thalamus cauterized		
	August 28	Blood pressure tracing	120	Bird in good condition
72	August 17, 1918	Cortez cerebri cauterized		
	July 3, 1920	Blood pressure tracing	122–140	Bird in good condition
73	August 17, 1918	Cortex cerebri cauterized		
	July 3, 1920	Blood pressure tracing	104–148	Bird in good condition
62	February 19, 1919	Cortez cerebri cauterized		
	July 3, 1920	Blood pressure tracing	102–124	
193	May 15, 1919	Gross traumatism of cerebellum		
	July 6, 1920	Bird recovered. Blood pressure tracing	96–102	Bird is tubercular

obvious disturbance in such an animal is complete blindness (at least temporarily) of the opposite eye. In some cases these birds go into a condition resembling complete decerebration (probably due to vascular disturbances in the remaining hemisphere). These animals will not feed themselves, assume a decerebrate attitude and die of starvation unless fed by hand. In this series of four birds two recovered and two

died of starvation. The blood pressure readings in the two birds that recovered were normal. The combination of hemi-decerebration and starvation led to lower blood pressure.

It was found, therefore, that no localized cerebral or thalamic injury led to permanent depression of the arterial pressure. Complete loss of either hemispheres, or hemispheres and thalamus, leads to distinct arterial depression.

Artificial stimulation of cerebral cortex. Electric stimulation of the cortex of the cerebral hemispheres gave a slight rise in blood pressure with no movements of the skeletal muscle. Stimulation was done under light ether anesthesia. Stimulation of the thalamus causes a sharp rise in arterial pressure, but also leads to muscular activity. Whether this rise is a true vasomotor reaction or a mechanical one due to striated muscle contraction was not determined, but Sachs and others have shown that vasomotor reflexes are readily induced by artificial stimulation of the thalamic nuclei.

DISCUSSION

The results given above lead to the suggestion that the cerebral hemispheres exert a continuous tonic activity on the mechanism whereby arterial pressure is maintained. Whether this be through the vasomotor, skeletal or some other systems individually or combined is not determined. Porter's findings on curarized decerebrate rabbits indicate a tonic action on the vasoconstrictor centers. The relatively slight influence of the cerebral hemispheres on the skeletal muscle of the pigeon[1] suggests that in this case lowered blood pressure is also due to a loss of vasomotor tone rather than to changes in the skeletal muscle.

The possibility of a depression of arterial pressure due to unknown changes in metabolism, after loss of the cerebrum, can not at present be excluded. Some evidence has been presented that this alone is not sufficient to bring about the vascular changes described, witness the negative effects of starvation, inactivity, etc. These experiments however do not conclusively exclude a contributing metabolic factor

[1] There are no cortical motor points in the cerebral hemispheres of the pigeon except possibly for the eye (Ferrier). Electric stimulation of the exposed cortex in the unanesthetized pigeon causes no muscular movements. Removal of the hemispheres likewise leads to no paralysis. These facts suggest that the fall in arterial pressure is not due to secondary changes in skeletal muscle.

after brain injury. Further studies in metabolism after cerebral lesions must be made in spite of the negative results reported by various observers.

However this may be, the inference can not be avoided that any functional depression of the cerebral hemispheres should be followed by lowered arterial tension. This might be due to sleep, anesthesia or destruction (provided there be no increase in intracranial pressure). Certainly there are differences in detail of the mechanisms in each case but it is noteworthy that in each case of cerebral depression there is lowered arterial pressure. No localized cerebral vasomotor centers are postulated. Indeed localized injuries of either hemispheres or thalamus caused no change of arterial pressure. The lowering of arterial pressure described follows the loss of large amounts of cerebral substance rather than the loss of particular areas of the hemispheres or thalamus. To this extent, this report reaffirms for the vasomotor mechanism, the old teaching of Flourens that, in the bird, the effects of cerebral injury are due not to the loss of local centers but are proportional to the quantity of brain tissue rendered non-functional.

SUMMARY

A method is described for studying the blood pressure in the pigeon.

The average pressure in the brachial artery of thirty-nine normal adult pigeons, under ether anesthesia, was 118 mm. mercury. The average limits of variations, due to variations in anesthesia, were 109 to 130 mm. Pressor and depressor effects on the blood pressure may be readily induced by stimulation of the spinal nerves. Ammonia to the nostrils causes a sharp rise in blood pressure. Respiratory waves and Traube-Hering waves of blood pressure occur as in mammals. The loss of small quantities of blood is quickly followed by compensatory changes bringing the pressure back to normal.

Starvation for three to seven days does not appreciably alter the pressure in normal birds.

Removal of the cerebral hemispheres in fifteen birds led to a fall of the average arterial pressure to 99 mm. (loss of 17 per cent). This lowered pressure persisted for time intervals up to four months after decerebration and never regained the level before operation. Removal of the cerebral hemispheres and thalamus leads to a similar or greater fall in arterial pressure varying as the body temperature varies. The greater the fall in body temperature, the greater the depression of the arterial pressure.

The poikilothermous condition in the bird, following excision of the thalamus, is not primarily due to lowered arterial pressure.

In the pigeon rendered poikilothermous by combined decerebration and destruction of the thalamus, the vasomotor responses to mechanical stimulation of spinal nerves, ammonia to the nostrils, and compensatory recovery of pressure after slight hemorrhages, are all depressed or take place more slowly, varying with the depression of body temperature.

The arterial pressure is not appreciably disturbed by removal of a single cerebral hemisphere, localized lesions of both hemispheres, or localized thalamic lesion (without cerebral destruction) provided these injuries are not associated with starvation.

These experiments suggest that the cerebral hemispheres and thalamus exert a continuous tonic stimulating action on the subcortical blood pressure regulating mechanism. This action is not one of localized cerebral centers but varies according to the amount of brain substance destroyed, rather than the particular area destroyed.

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EXPERIMENTAL STUDIES IN DIABETES

Series II. The Internal Pancreatic Function in Relation to Body Mass and Metabolism[1]

5. The Influence of Fever and Intoxication

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The accuracy with which the metabolism of cold-blooded animals can be regulated through the temperature was one of the reasons for the attempt to produce diabetes in them at the outset of this investigation. When the production of a satisfactory type of diabetes proved impossible, the research was thrown back entirely upon mammalian experiments, where the disturbing factors are greater. Some observations were made concerning the effects of fever and of external cold.

No discussion of the literature will be undertaken, beyond reference to a review (1) of the earlier literature, and a more recent paper by Freund and Marchand (2), which show that elevation of body temperature is generally accompanied by elevation of blood sugar, but terminal collapse may be accompanied by hypoglycemia; the rise of body temperature in itself tends to increase sugar tolerance, and lowered tolerance or glycosuria are attributable to intoxication or sometimes to pancreatic damage. Infections are known to be one of the worst agencies in aggravating human diabetes. The effect of aseptic elevation of temperature seems not to have been tested. It was desired in the present research to compare several forms of infectious and non-infectious fever in their influence upon partially depancreatized dogs. The only results actually permitted by circumstances consisted in records of a number of animals which acquired chance infections, and one research concerning the gas bacillus. The observations will be classified according to the site of the infections.

[1] The first four papers of this series are published in the American Journal of the Medical Sciences.

Distemper. For this purpose canine distemper is closely comparable to human tuberculosis. Diabetes plainly increases the susceptibility of dogs and still more of puppies to this infection, in the sense that they both acquire it and succumb to it more easily. Tuberculosis seriously lowers the food tolerance and increases the tendency to glycosuria and hyperglycemia in human patients even in the earlier non-febrile stages, and this effect becomes still greater in the febrile stage. In numerous observations in dogs covering all stages of distemper and all degrees of diabetic tendency, precisely the opposite effect has been found. It is true that distemper is characterized by early failure of appetite and digestion. The resulting emaciation constitutes a very radical undernutrition treatment, and a similarity thus exists to Joslin's frequently quoted Case R (3), in which the emaciation of tuberculosis on a regulated diabetic diet evidently improved the assimilation. But the infection has been observed in dogs with definitely known tolerance, which continued for some time to take a diet close to the limits of tolerance. There have been other examples such as dog C3-77, 1 year old, weighing 10.5 kilos, and subjected on April 13, 1916, to the removal of all but $\frac{1}{2}\frac{1}{2}$ to $\frac{1}{2}\frac{1}{8}$ of the pancreas (estimated remnant 1 gram).[2] Glycosuria began immediately and by April 17 had reached 2.9 per cent, fasting. It then ceased as the first signs of distemper appeared in the form of conjunctivitis. The dog refused food and wasted away in the usual manner till killed on May 7, at a weight of 6.3 kilos. The pancreas remnant weighed 1.35 grams. The islands showed very slight vacuolation in a few cells, such as might persist from the initial glycosuria, but far less than would result from 3 weeks of active diabetes. The remnant was so small and the diabetic tendency so strong that sugar-freedom on fasting would have been impossible if the infection had introduced any aggravation, but the result seemed to be identical with that in a non-infected animal.

Pneumonia. Dog B2-18, after removal of $\frac{1}{1}\frac{3}{3}$ of the pancreas on December 2, developed moderate glycosuria on diets containing carbohydrate, in a cold environment. December 6 the dog was found to be unwell and febrile, but continued to eat the diet through the illness to December 9, and the glycosuria continued unchanged. Death occurred from double pneumonia on December 13. The autopsy urine contained 1.65 per cent sugar. The vacuolation in the pancreatic islands was similar to that of non-infected dogs at the same stage.

[2] All operations were performed under ether anesthesia.

Dog C3-73 similarly underwent operation leaving $\frac{1}{10}$ to $\frac{1}{11}$ of the pancreas on April 3, and died of pneumonia on April 18. The final urine on April 17 contained heavy sugar, but death was apparently preceded by anuria.

Dog D4-72 was left with a remnant of $\frac{1}{9}$ to $\frac{1}{10}$ of the pancreas on January 12, and died of pneumonia on January 19. The appetite continued and the glycosuria was not appreciably changed with the onset of fever. Nothing was eaten after January 17. The autopsy urine still contained a trace of sugar. There was thus a diminution resembling the effect of ordinary fasting, not the great increase which usually accompanies infection in any severe human case.

Cat A1-93 was left with a remnant of $\frac{1}{5}$ to $\frac{1}{6}$ of the pancreas on January 21, and died of pneumonia on January 26. Because of refusal of food, there was only a transitory trace of glycosuria, as would be the case in a non-infected cat fasting after such an operation.

Other examples might be given in which infection failed to cause glycosuria when the removal of pancreatic tissue was not quite sufficient to produce it in a non-infected animal, and still others in which extreme prostration prevented glycosuria which must otherwise have occurred. In no instance was any evidence of aggravation of diabetes seen.

Pleurisy. Dog B2-22 had been used in another department for collection of leukocytes by intrapleural injections, and on December 8, $\frac{9}{10}$ of the pancreas was removed without knowledge of the existence of a large purulent pleurisy. Fever, malaise and other symptoms were found after the operation. The dog ate small quantities of bread and milk on December 9 and 10, and glycosuria of 2 to 3 per cent continued to December 12. Death occurred with sugar-free urine on December 13.

Subcutaneous abscesses. In connection with subcutaneous injections and other procedures a considerable number of abscesses have been observed in dogs with various degrees of diabetic tendency. The infections themselves have been of varying magnitude, from small collections causing no systemic symptoms to large ones accompanied by depression, anorexia and fever above 105°F. The organisms present were sometimes identified as staphylococci, streptococci or mixed bacilli. The same rule held as above, namely, that glycosuria might cease with fasting and prostration, or in less extreme cases might continue unchanged, but a marked aggravation such as is familiar in human cases was never seen.

Infected glands. Dog D4-92 on February 5, 1917, was subjected to removal of all but $\frac{1}{8}$ to $\frac{1}{9}$ of the pancreas. Bread and soup were eaten on February 8, and 100 grams glucose added on February 9, still without glycosuria. Thereafter nothing was eaten and remarkable symptoms of confusion and ataxia appeared, increasing on February 12 to general convulsions and suggesting rabies. The dog was chloroformed on February 13, and the brain examination was negative for meningitis or Negri bodies. The autopsy otherwise was negative except for a little creamy pus found oozing from between the pectoral muscles, leading to caseous-appearing glands in and about both axillae. The type or origin of the infection was not determined. Glycosuria remained absent.

Rabies. Several partially depancreatized dogs died of rabies. One of these was dog B2-02, which, as previously mentioned (4), had been carefully studied and was known to have latent diabetes. No glycosuria resulted in any instance. The negative results were of interest in a condition attended with such pronounced nervous excitation, and in which convulsions may give rise to very marked hyperglycemia (5).

General peritonitis. This naturally involves cessation of glycosuria in most cases because of fasting and prostration. With sufficiently large experience, examples are encountered which indicate that the infection in itself does not alter the glycosuria. Some such were described previously (6), and the following have been observed since.

Dog B2-13. November 24, 1913, removal of $\frac{13}{14}$ of pancreas. There was glycosuria of 0.25 per cent in 60 cc. of urine following operation, and 0.2 per cent in 330 cc. after eating 150 grams meat on November 27. Otherwise there was fasting and freedom from glycosuria up to death from peritonitis on November 29.

Dog B2-21. December 4, 1913, partial pancreatectomy leaving a remnant of $\frac{1}{13}$ to $\frac{1}{14}$. After bread feeding on December 5, heavy glycosuria began, and continued to death from peritonitis on December 11. Bread was eaten daily to December 9. The autopsy urine was 100 cc., with 2.85 per cent glucose. The pancreatic islands showed the slight vacuolation proper to this early stage of diabetes.

Cat A1-82. December 19, 1913, removal of $\frac{7}{8}$ of pancreas. The cat refused food but acted well and cleaned her fur up to December 22, and died of peritonitis December 23. Glycosuria began with a faint reaction on December 21, rose to 2.5 per cent on December 22, and was 4 per cent in the last 55 cc. of urine on December 23. The pancreatic islands showed incipient vacuolation in a minority of cells.

Cat A1-87. January 8, 1914, removal of $\frac{5}{6}$ of pancreas. There was slight continuous glycosuria with very little eating from January 9 to death from peritonitis on January 12. The islands were free from visible vacuolation, as would be expected in a non-infected animal with such brief and mild diabetes.

Peritoneal and pancreatic abscesses. In addition to previous examples (6), the following may be mentioned.

Dog D4-65. December 21, 1916, an Eck fistula was unsuccessfully attempted, and some sutures were left on the veins. January 2, 1917, $\frac{6}{10}$ of the pancreas was removed. The dog was lively and immediately developed glycosuria on bread feeding. This ceased on January 8, and was restored by addition of 100 grams glucose daily. On January 10 emaciation, fever and weakness first became noticeable, but the diet was still eaten without change in the heavy glycosuria. With a change of diet to 1 kilo of beef lung on January 12 glycosuria immediately ceased. Beginning January 14 food was refused, and the dog was killed January 15, at a weight of 9.8 kilos as opposed to an original 13.5 kilos. A grape-sized abscess of creamy pus at the site of the Eck operation was the only discoverable cause of death. It had not altered the course of the diabetes from what is the rule with non-infected dogs under the same conditions.

Dog D4-57. December 7, 1916, removal of $\frac{4}{5}$ of the pancreas. The usual complete absence of diabetes was demonstrated thereafter. March 1, 1917, additional tissue was removed, possibly sufficient for mild diabetes. Malaise, fever and complete refusal of food followed. Glycosuria was absent on March 2, 3 and 4, but present just before death on March 5 to the extent of 0.8 per cent in 182 cc. of urine. The plasma sugar at this time was 0.625 per cent, CO_2 capacity 69.2 vol. per cent. Autopsy showed the pancreas remnant to be riddled with small abscesses, and though there was no necrosis the inflammatory injury had evidently brought on a severe degree of diabetes which would otherwise have been lacking. Infection has never been found to produce acetonuria or other evidences of acidosis in any animal.

Dog F6-14 was subjected to removal of about $\frac{7}{8}$ of the pancreas in three successive operations. January 31, 1918, an attempt was made to produce diabetes by circulatory stasis of the remnant, as described in a later paper. Only slight and transitory glycosuria resulted on a diet of bread and soup with 100 grams glucose. February 8, operation showed an abscess containing about 5 cc. of creamy pus between the pancreas and the duodenum. The cavity was cleaned and stasis repeated. Glycosuria was still impossible to maintain, and on March 9 stasis was applied for a still longer time, no infection being found. Glycosuria was then continuous up to March 19 on bread diet with 100 grams of glucose, but ceased then on plain bread and soup feeding. March 20 the abdomen was again opened, and the pancreas was found buried in a large mass of adhesions, which when delivered outside and opened was found to contain a very large abscess. The pancreas remnant, which in its whole length formed one wall of the abscess, was much inflamed but not digested. Nothing was done except the cleaning up of the infection, and the tolerance continued exactly as before; i.e., glycosuria was absent on bread feeding and present with addition of 100 grams of glucose. On April 10 the abdomen was again opened, and a tiny abscess in the omentum appeared as the only remains of the previous infection. Stasis was again applied to the pancreas remnant, and the dog died within 24 hours, whether from infection or from pancreatic intoxication was undetermined.

The long history of this animal, with alternate presence and absence of a low grade infection, seems to prove that in this instance the infection had no important influence upon the tolerance.

Other examples of this sort might be given. There was particular interest in the cases in which diabetes was produced by inflammation instead of by simple resection, because of the supposed closer imitation of the clinical etiology. It was conceivable that inflammation might damage the islands in function as well as in structure, so as to render them more susceptible to toxic influences. The negative results raised a question concerning some fundamental difference between clinical and experimental diabetes, or a mere difference of constitutional reaction to infection on the part of man and animals. The above general observations sufficed positively to exclude any such marked aggravation of diabetes in animals as occurs regularly in human cases with the fever and intoxication accompanying infection. There remained the need of making a more exact test of the tolerance in experimental diabetes as influenced by infection, and this opportunity was afforded by the experiments with the gas bacillus reported in the next paper. These seemed to indicate that the difference between clinical and the experimental diabetes may be one of degree rather than of kind.

CONCLUSIONS

1. The serious aggravation of diabetes, which occurs almost invariably in human cases in the form of a strongly increased tendency to glycosuria and acidosis, is never seen in dogs. Even when the infection is an abscess bordering or invading the pancreatic tissue, no influence is evident beyond that explainable by direct injury of parenchyma. This contrast between clinical and experimental diabetes is very marked, but according to the more exact tolerance tests in the succeeding paper it may represent a difference of degree rather than of kind.

2. Infection and fever have also no specific influence in diminishing the diabetic tendency of dogs. Care is necessary in interpreting such observations, in order not to confuse the direct influence of fever or infection with the consequences of fasting or prostration, which tend so strongly to suppress glycosuria in dogs. One suggestion of a constitutional difference between species may be found in the tendency of human patients to acidosis and of dogs to cachexia.

3. The aggravation of human diabetes is a reaction to intoxication rather than to fever, as shown by its occurrence in the afebrile stage

of tuberculosis and by other evidence. The present observations concerning infectious fever, with the previous ones concerning the pyrexia of exercise in dogs, prove that no specific aggravation of diabetes or lowering of tolerance results from the metabolic alteration attendant upon elevation of body temperature in experimental animals.

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EXPERIMENTAL STUDIES IN DIABETES

Series II. The Internal Pancreatic Function in Relation to Body Mass and Metabolism

6. Gas Bacillus Infections in Diabetic Dogs

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In the course of this diabetic research four dogs died of gas bacillus infection. Two of these instances were merely post-operative peritonitis, with the gas bacillus predominating.

Another was dog E5-74, a bulldog mongrel, aged 5 years, in splendid condition, weighing 20.7 kilos. July 3, 1917, two-thirds of the pancreas were removed, and most of the remnant was cut off from duct communication.[1] On July 20, the remnant was subjected to circulatory stasis for 1½ hours. Glycosuria was present on bread diet with addition of 150 grams of glucose daily up to July 30, when it ceased, and the dog was turned loose in the yard with other dogs on bread diet. The behavior meantime was normal. About August 5, swelling in the neck became noticeable and the dog was slightly depressed. August 7, the swelling was much larger, and a deep abscess was opened surgically, releasing a considerable quantity of thick bloody pus containing gas bubbles. Cultures from some of the necrotic debris gave a pure growth of B. aerogenes capsulatus. Death occurred August 9, after still greater invasion of the neck. There was no glycosuria or vacuolation of pancreatic islands, though both these conditions might have been prevented by the terminal emaciation and cachexia.

Dog B2–49, a female mongrel aged 3 years, in medium nutrition at a weight of 25.4 kilos, underwent partial pancreatectomy on March 27, 1914, leaving a remnant of ¼ to ⅕ about the main duct. As previously mentioned (1), prolonged carbohydrate over-feeding was used in the attempt to break down tolerance, 300 or 400 grams glucose

[1] All operations were performed under ether anesthesia.

being added to the diet of bread and soup daily. There was neither glycosuria, diarrhea nor any evident ill-health, until the animal was unexpectedly found dead on May 9. There were adhesions in the right pleura, from supposedly sterile intrapleural injections in another department long before the animal was taken for diabetic work, and these probably furnished the start of the infection. Gas bacilli were found abundantly in smears and cultures from the principal viscera, seemingly alone. The greatest change was in the spleen, which was blown up to resemble a lung. The pancreas remnant was normal and free from vacuolation. In other words, neither the prolonged sugar feeding nor the infection produced any change in either islands or acini in this non-diabetic animal.

A study of gas bacillus infections was in progress at this time under the direction of Dr. Carroll G. Bull. As gas bacillus infections are rare in dogs, it was decided to follow up the above accidental observations by experiments upon diabetic dogs with a view to two questions; first, whether such animals are abnormally susceptible to such infections by reason either of the excess of circulating sugar or a specific diabetic lowering of resistance; second, whether an aggravation of the diabetes is demonstrable by such infections. The conditions were favorable for both problems; for the first problem because the growth of the gas bacillus is notably favored by the presence of sugar, and some test was thus afforded of the theory of excess of sugar as the cause of diabetic susceptibility to infection; for the second problem because of the proof (2) of the production of a soluble toxin by the gas bacillus, so that a systemic effect capable of influencing the diabetes might be expected from a local infection. Accordingly experiments with intramuscular injections of pure cultures of the Welch bacillus were performed upon three diabetic dogs. The dosage used was intended to produce the maximum possible local effects and general intoxication without excessive prostration. Still larger doses might have overwhelmed the animals suddenly and completely, but would thus have demonstrated nothing of value for either bacteriology or diabetes.

In the first experiment (table 1) glycosuria practically ceased with the anorexia accompanying infection on September 12, as usual with dogs and in contrast to the usual aggravation of symptoms in human patients with infection. Nevertheless a lowering of tolerance was shown by the heavier glycosuria when the diet was taken on September 13. Illness and fasting again resulted in sugar freedom after the injection of September 14, but a more marked lowering of tolerance was evident in

TABLE 1

Dog E5–88. Male; Welsh terrier mongrel; old but strong, in excellent nutrition; weight 11.25 kilos. August 24, 1917, removal of pancreatic tissue weighing 18 grams. Remnant about main duct estimated at 1.6 grams ($\frac{1}{12}$ to $\frac{1}{13}$). The diabetes was checked by undernutrition and fasting, so that at the time of the experiments the dog weighed 9.5 kilos and took a bread and soup diet with very slight glycosuria.

DATE	RECTAL TEMPERATURE	URINE		REMARKS
		Volume	Glucose	
1917	*°C.*	*cc.*	*per cent*	
September 10.....		660	0.3	Bread and soup diet
September 11 . ..	38.7	450	0.4	
September 12 . ..		510	Trace	At 10:45 a.m. injected 0.1 cc. per kilo of broth culture of Welch bacillus intramuscularly right thigh. Marked local edema and swelling. Dog depressed; ate nothing
10:00 a.m. . .	38.8			
1:15 p.m.....	39.7			
3:30 p.m.....	40.7			
5:30 p.m.....	40.4			
September 13.....				Thigh still swollen. Dog unwell but took entire diet, part forcibly
9:00 a.m.....	39.7	880	2.6	
September 14 . ..				9:30 a.m., injected 0.3 cc. per kilo of broth culture of Welch bacillus intramuscularly left thigh. Much local swelling. Dog ill and feverish; refused diet but ate a little meat
9:00 a.m. . .	38.3	670	2.8	
September 15.....	39.8	320	1.4	Refused all food
September 16.....		425	0.3	Refused all food. Great edema and crepitation, extending into scrotum
September 17.....		510	Trace	Refused food
September 18.....		650	0	Refused food
September 19.....		420	0	Refused food
September 20.....		400	Trace	Ate a trifle of meat and bread
September 21.....	39.5	450	0	Ate very little of meat
September 22... .		480	Trace	Ate more meat. Much swelling and gas in leg
September 23.....		460	0.6	Acting better. Ate more meat
September 24.....		400	1.2	Ate some bread and meat
September 25... .		500	2.1	Ate full diet
September 26. ...		700	2.9	Ate full diet
September 27.....		630	3.4	Ate full diet
September 28.....		610	3.1	Ate full diet
September 29.....	38.8	1200	2.2	Both thighs have discharged necrotic material, leaving granulating ulcers. Dog lively and vigorous

the glycosuria from meat alone on September 22 and 23, and the heavier glycosuria thereafter on the regular bread diet.

Dog E5–89. Male; mongrel; age 3 or 4 years; good condition; weight 14 kilos. August 24, 1917, removal of pancreatic tissue weighing 25 grams. Remnant about main duct estimated at 1.6 gram ($\frac{1}{18}$ to $\frac{1}{17}$). Severe diabetes being thus produced, the glycosuria was raised to a maximum by a diet of bread and soup with 100 grams of glucose daily.

September 7, at a weight of 12.6 kilos, 0.25 gram additional pancreatic tissue was removed for microscopic examination.

September 14, at the same weight, 0.1 cc. broth culture of Welch bacillus per kilo was injected intraperitoneally, in order to test whether under these conditions of maximum glycosuria and hyperglycemia infection would be possible. The rectal temperature rose within an hour to 39.4°C. After 6 hours it was 39.5°, and the next morning 39.6°. It then subsided, and after one day of slight malaise the dog continued to eat his diet. The glycosuria continued unchanged except for a diminution on the one day of anorexia.

September 24, an injection of 0.3 cc. of broth culture per kilo was given intramuscularly in one thigh. The usual local and general symptoms occurred in intense form. September 29, with very large swelling and gas formation present in the leg, a blood culture was taken and proved negative. The dog regained a little appetite, taking small amounts of meat and bread daily, but great anemia was shown by blood examinations, the corpuscle volume being only 10 to 12 per cent. Death occurred October 5. Glycosuria remained heavy throughout, including the autopsy urine. The gross autopsy showed no visceral changes suggestive of gas bacillus invasion. Cultures of blood and tissues were also negative for this organism.

The pancreas remnant, normal in appearance and consistency, weighed 1.7 grams. Microscopically, the tissue removed August 7 showed a very early stage of vacuolation of islands. The remnant at autopsy showed a late stage of the process; islands were scarce and small, and the great majority of the cells (probably all of the beta cells) were maximally vacuolated.

In this experiment the production of a general infection with the gas bacillus proved impossible notwithstanding the severe diabetes and intense glycosuria. The intraperitoneal injection failed entirely. The intramuscular injection caused extensive sloughing which destroyed most of the musculature of the limb, but death resulted only from the immediate and subsequent toxic effects and not from systemic invasion.

Dog E5–90. Male; mongrel, age 3 or 4 years; medium nutrition; weight 10.25 kilos. August 24, 1917, removal of pancreatic tissue weighing 20.3 grams. Remnant about main duct estimated at 1.6 gram ($\frac{1}{18}$ to $\frac{1}{14}$). On bread diet there was a diminishing glycosuria which ceased August 31, probably because of hypertrophy of the pancreas remnant, which subsequently at autopsy was found to weigh 5.4 grams. Beginning September 8 the addition of 100 grams glucose restored a heavy glycosuria, and the tolerance was brought down so as to produce a perma-

nent mild diabetes. During October sugar freedom was maintained on a diet of 500 grams lung and 100 grams suet, except for occasional days on which it was proved that bread and soup diet would promptly bring back a mild glycosuria.

October 25, an intravenous glucose tolerance test was performed, by injection of 25 cc. of 10 per cent solution of Merck anhydrous glucose every 15 minutes (1 gram per kilo per hour, on 10 kilos weight) for 3 hours, according to the method described elsewhere (3). Catheterization was performed and blood samples taken before the first injection and at hourly intervals thereafter as shown in table 2.

October 26, 4 cc. of a heavy broth culture of the Welch bacillus were injected intramuscularly in the right thigh. The rectal temperature rose to 41.1°C. that evening and was 39.6° the next morning. The dog refused food and there was no glycosuria. By October 31 there was partial recovery and part of the diet was eaten. The weight had fallen from 10 kilos to 9.75.

TABLE 2

BLOOD			URINE						REMARKS
Plasma sugar			Volume			Glucose			
October 25	November 1	December 18	October 25	November 1	December 18	October 25	November 1	December 18	
per cent	*per cent*	*per cent*	*cc.*	*cc.*	*cc.*	*grams*	*grams*	*grams*	
0.164	0.133	0.122				0	0	0	Before injection
0.333	0.400	0.384	5	41	14	0.034	0.450	0.320	End of 1st hour
0.323	0.400	0.500	14	42	50	0.080	1.150	2.000	End of 2nd hour
0.213	0.216	0.455	95	14	26	Faint	0.360	0.680	End of 3rd hour
0.081			400	150	30	Slight	0.690	0	Next morning

November 1, an intravenous glucose test was performed, identical with the dosage on October 25. A lowering of tolerance was indicated by both the blood and urine analyses.

November 14, 4 cc. of the gas bacillus culture were injected in the other thigh. Local edema, gas formation and necrosis occurred as before, but the general symptoms were less. The temperature on the morning of November 15 was 38.8. The dog ate well and showed a spontaneous glycosuria of 2.15 per cent in 340 cc. urine. The following day it was 0.48 per cent in 530 cc. urine, and then disappeared.

Later the dog was unwell and ate poorly, probably on account of secondary infection of the sloughing area in the leg. No further glycosuria developed, and by December 18 the animal was again in good general health at a weight of 10 kilos, though a large open ulcer was still present.

December 18, the animal was given the same intravenous glucose injections as before. A reduced tolerance was still indicated, either because of the ulcer or because the lowering due to infection was permanent, as it is in many human cases.

An accidental or spontaneous fall of tolerance is probably excluded by the fact that the dog was kept on the lung and suet diet till March 27 without glycosuria. He was then used for other experiments, and no further tolerance test was made.

CONCLUSIONS

1. Intramuscular injections of pure cultures of B. aerogenes capsulatus produced local necrosis and gas formation in partially depancreatized diabetic dogs. Systemic or peritoneal infection was not obtained. The observations failed to indicate any lowering of resistance in these animals due either to the diabetes itself or to the excess of sugar in the body fluids. The latter point is further emphasized by the fact that the reactions were essentially similar in the first dog with mild glycosuria, in the second dog with heavy glycosuria, and in the third dog free from glycosuria. These results agree with the general experience that such animals ordinarily bear operations well and their wounds heal normally.

2. A lowering of tolerance by infection was demonstrable both by feeding and by intravenous glucose tests. Though this influence is less in animals than in human patients, the difference seems to be one of degree rather than of kind.

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STUDIES IN EXPERIMENTAL TRAUMATIC SHOCK

I. The Basal Metabolism

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The marked loss of body temperature is one of the most striking features of traumatic shock. To study this, as well as to investigate the relationships of metabolism and ventilation to the sudden changes in blood pressure, was the purpose of these experiments. The problem was approached through the gaseous exahange.

The literature upon this subject is very meager. Guthrie (1), reported no consistent findings in either O_2 absorption or CO_2 output with animals under ether anesthesia. Henderson, Prince and Haggard (2), in a preliminary note, mention a marked drop in metabolism in two dogs in shock, but give no details of experiments. Roaf (3), working on decerebrate cats, states that his experiments tend to show that fall of blood pressure does not markedly reduce the production of CO_2.

Methods. Cats were used that had not eaten for 24 hours. They were anesthetized by urethane given by mouth, 8 cc. of a 25 per cent solution per kilo of body weight, and only when fully anesthetized were they stretched out on an animal board. The temperature was recorded through a rectal thermometer graduated to tenths, and was kept as nearly constant as possible by means of an electric heating pad.

The operation consisted of inserting a trachea cannula and cannulae in two arteries, usually both carotids, and also usually one in the external jugular vein. One carotid cannula was then attached to a mercury manometer and blood pressure tracings begun. In some experiments 10 cc. of arterial blood were now removed; in most cases blood was taken only after several respiration samples had been obtained.

The inspired air was room air. The samples of expired air were obtained in two 8-liter copper spirometers. The valves used were Tissot valves, attached directly on the T-shaped glass tracheal cannula. The air sample was promptly withdrawn from the spirometer and preserved under pressure in the usual type of glass sampling tube. Gas analyses were made in the Haldane apparatus, and careful checks of room air were made before samples were analyzed. Urinary nitrogen determinations were not made (4).

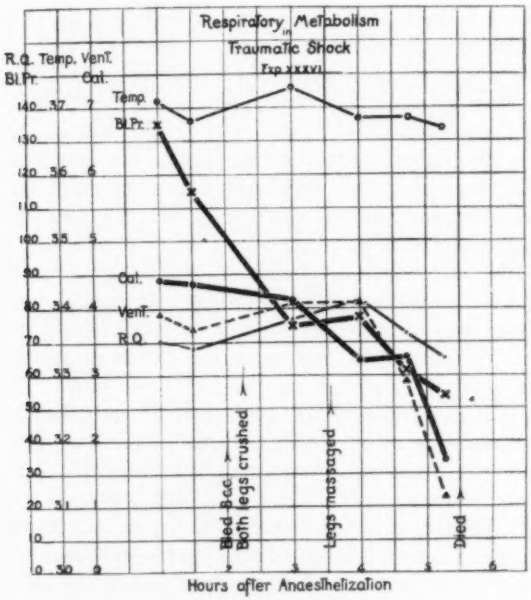

Fig. 1. Vent. = Ventilation volume per minute in 100 cc.
Cal. = Total calories per hour.
R. Q. = Respiratory quotient.

To produce shock the thigh muscles of both hind legs were thoroughly crushed (5). When the blood pressure fell below 70 mm. Hg. systolic and stayed below that level, the animal was considered to be in a state of shock. No attempt was made to measure blood flow, as all extra manipulation was rigidly avoided.

The experiments may be grouped as follows:

I. Normal controls. Table 1.

II. The simple traumatizing of muscle tissue and the study of respiratory metabolism before and after the resulting drop in blood pressure. Tables 3 and 4.

III. The production of traumatic shock and the subsequent raising of the blood pressure by transfusion with cat's blood. Table 5.

IV. The effect on metabolism of hemorrhage when it alone caused a marked fall of pressure. Table 2.

V. The production of a low blood pressure without shock by increasing pericardial pressure. Table 6.

Discussion. Table 1 shows that the metabolism following urethane anesthesia when given by mouth remains quite constant for 4½ hours at least. It may then fall to a lower level. Raeder (6) kept rabbits alive for over 3 days by administering urethane subcutaneously. He came to the conclusion that the total metabolism fell only about 2 per cent an hour, and that it was a satisfactory anesthetic to use in studying respiratory metabolism.

The level of the basal metabolism during shock has fallen in all but one case below the value found before the muscles were crushed. In six cases of mild shock (table 3) the average reduction in calories was −19 per cent, and in eight cases of severe experimental shock (tables 4 and 5) the average fall was −30 per cent. This average does not include experiment LIII in which the metabolism rose. Likewise in five experiments in which pericardial pressure was increased (table 6) and the blood pressure so reduced, there was a prompt drop (fig. 2) to an average of −31 per cent below the former height. In general the "critical level" of blood pressure for the metabolism, as with the development of diminished alkaline reserve, is at 75 or 80 mm. Hg. At that level the metabolism may be within normal limits or it may be considerably reduced. Usually when a normal value is found, the blood pressure has been stationary or rising; but when the metabolism figures are reduced the blood pressure is falling. With a pressure below 75 mm. Hg., the calorie production has, with but one exception, been reduced.

While the reduced blood pressure undoubtedly has a great deal to do with the fall of metabolism, it is probably not the whole story. Experiment XXXIV, table 2, shows that a low blood pressure, following hemorrhage alone, may be associated with only a slight drop in metabolism. With a blood pressure of 55 to 62 mm. Hg. immediately

after bleeding the metabolism was only −10 per cent; and in the third period, although the rising blood pressure had been below 80 mm. Hg. for 45 minutes, the metabolism was only −1 per cent. So also in the last period after the pressure had been 50 mm. Hg. for 20 minutes, but was rapidly rising at the time the period was taken, the metabolism was only −7 per cent.

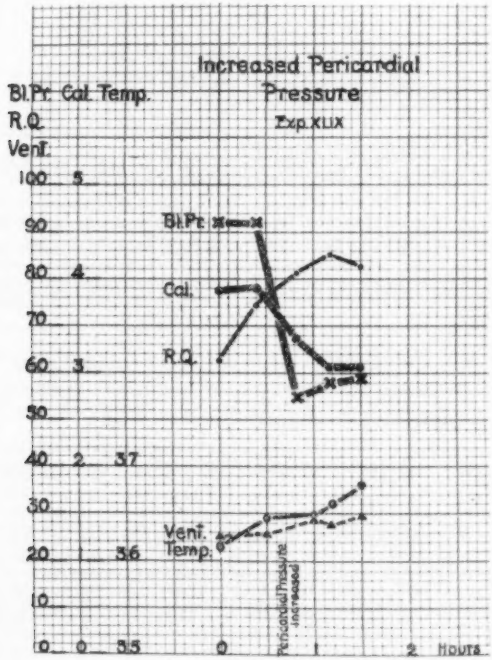

Fig. 2. Vent. = Ventilation volume per minute. The figure should be multiplied by ten.

There are also examples of blood pressures above the critical level associated with reduced metabolism. In experiment XXXIII, table 2, the second period shows a sudden drop of 22 per cent in metabolism 20 minutes after bleeding 15 cc., while later a return to normal limits occurred even though muscle injury was done. This bleeding only caused an immediate drop in blood pressure from 110 to 90 mm. Hg.,

TABLE 1

Respiratory metabolism; controls

EXPERIMENT NUMBER, WEIGHT, DATE	TIME OF PERIOD	RESPIRATORY EXCHANGE PER MINUTE		RESPIRATORY QUOTIENT	CALCULATED CALORIES PER HOUR		RESPIRATORY RATE PER MINUTE	RESPIRATORY VOLUME PER MINUTE	RECTAL TEMPERATURE	BLOOD PRESSURE	TIME OF ANESTHETIZATION	REMARKS
		CO_2	O_2		Calories	Variation						
		cc.	*cc.*			*per cent*		*cc.*	°*C.*	*mm. Hg.*		
Experiment XXVI, 3/28/19, 3200 grams, ♂	11:35	19.4	28.3	0.69	7.83		62	583	38.0	95–105	10:52	
	12:07	21.2	27.9	0.76	7.90			615		110		
	12:50	20.2	28.6	0.71	8.03		44	587	37.0	120–110		
	2:00	19 9	27.7	0.73	7.78	−1	46	606	36.5	110		
	3:00	22 0	28.8	0.76	8.18	+4	*	694	36.8	115–120		
	4:00	19.7	26.1	0.75	7.38	−6	46	474	36.8	120		
	5:10	18 7	26.6	0.70	7.45	−5		447	37.6	110		6 hours, 20 minutes after anesthesia
Experiment XXVII 3/31/19, 3100 grams, ♂	12:23							478	36.8	160	11:30	Blood CO_2 comb. P. 47.1
	1:23	19 8	25.9	0.76	7.35		20	369	36.4	150		
	2:25	19.8	26.1	0.76	7.39			427	36.6	130		
	3:30	18.7	25.8	0.72	7.25	−2		366	37.0	135		
	4:25	18 9	25.5	0.74	7.19	−2		342	37.0	135		Blood CO_2 comb. P. 53.8
	5:25	17 8	24.4	0 73	6 84	−7	27	328	36.5	115		6 hours after anesthesia
Experiment XLVI, 7/15/19, 1800 grams, ♂	11:03	12.1	14.1	0.85	4.10		51	483	36.4	108	10:10	
	11:22	11 3	14 8	0.77	4.19		53	457	36.4	106		
	12:02	9 7	13.3	0.73	3.73	−10	48	357	36.6	95		
	1:15	10 2	13.8	0.74	3.88	−6	45	414	36.8	102		
	2:02	10.1	13.5	0.77	3.81	−8	48	376	36.8	110		
	3:33	8 7	11.7	0 75	3.30	−20	44	350	36 2	100–90		5 hours after anaesthesia
	4:19	8.6	12.2	0.71	3.43	−18	45	380	36.4	100		
	5:11	8.1	11.4	0 71	3.20	−23	43	357	36.8	95		7 hours after anesthesia

Experiment LIX, 12/12/19, 3500 grams, ♀	11:09	17.0	24.6	0.69	6.91			659	38.2	107	9:50	
	11:30	18.5	25.2	0.73	7.07		44	809	38.0	105		11:50–12:00, Bled 25 cc. and transfused with 30 cc. citrated blood
	3:02	13.3	21.1	0.63	5.92	−15	36	443	38.0	100		
	3:25	14.8	22.0	0.67	6.15	−12	38	492	37.9	106		5½ hours after anesthesia
Experiment L, 3/17/20, 3000 grams, ♂	2:00	18.6	26.9	0.69	7.55			577	37.4	100	1:00	Cat had severe dyspnea before observations started
	2:20	19.5	25.3	0.77	7.18		36	554	37.3	100		
	3:00	19.1	23.5	0.81	6.75	−8	36	540	37.3	90		2:10, Blood samples taken, and blood replaced by transfusion
	4:00	19.1	24.9	0.77	7.08	−4	36	524	37.6	94		
	4:57	19.3	25.1	0.77	7.13	−3	36	547	37.6	115		
	5:36	17.6	24.6	0.72	6.89	−6	36	455	37.5	122		
	6:00	17.0	24.0	0.71	6.73	−8		409	37.5	112		
Experiment LVIII, 4/27/20, 2900 grams, ♂	12:47	14.5	19.3	0.75	5.46		24	594	37.4	100	11:35	1:00, Cat vomited
	1:11	15.1	21.7	0.70	6.10		22	474	37.5			2:10, Bled 25 cc. and blood replaced by transfusion. Cat vomited
	2:25	18.8	25.0	0.75	7.07	+21	20	595	37.5	110		
	3:34	17.4	24.3	0.72	6.81	+18	32	548	37.6			
	4:15	17.0	23.4	0.73	6.56	+13	32	525	37.9	120		3:20, Cat vomited
Experiment LXIX, 5/27/20, 2700 grams, ♀	12:25	18.4	23.6	0.78	6.71			465	37.8	127	11:15	12:55, Bled 25 cc. and blood replaced by transfusion
	12:40	14.3	19.6	0.73	5.51		18	362	37.5	118		
	1:20	15.3	20.3	0.75	5.73		24	396	37.9	106		
	2:27	15.5	20.4	0.76	5.78	−3	27	417	37.9	95		Blood clotted repeatedly in cannula during experiment
	3:06	17.2	21.9	0.78	6.25	+5	28	473	38.0	104		
	3:43	14.0	20.0	0.70	5.60	−6	22	399	38.0	104±		
	4:10	14.1	19.1	0.74	5.38	−10	30	461	38.1	110±		
Experiment LXX, 6/1/20, 3000 grams, ♀	11:37	14.2	21.5	0.66	6.03		22	467	37.4	144	10:30	
	12:47	18.6	25.1	0.74	7.08		40	700	37.6	138±		
	1:34	18.5	25.0	0.74	7.03	+7		666	37.7	145		
	2:15	18.2	23.4	0.78	6.67	+2	44	660	38.4	140±		Cat overheated
	3:45	19.1	28.0	0.68	7.85	+20	40	719	37.7	156		

* Dyspnea.

TABLE 2

Respiratory metabolism; hemorrhage

EXPERIMENT NUMBER, WEIGHT, DATE	TIME OF PERIOD	RESPIRATORY EXCHANGE PER MINUTE		RESPIRATORY QUOTIENT	CALCULATED CALORIES PER HOUR		RESPIRATORY RATE PER MINUTE	RESPIRATORY VOLUME PER MINUTE	RECTAL TEMPERATURE	BLOOD PRESSURE	TIME OF ANESTHETIZATION	BLOOD CO_2 COMBINING POWER	REMARKS
		CO_2	O_2		Calories	Variation							
		cc.	*cc.*			*per cent*		*cc.*	*°C.*	*mm. Hg*			
Experiment XXXIV, 4/19/19, 2700 grams, ♀	11:15	14.7	20.4	0.72	5.73		44	523	36.2	102	9:45	48.3	Experiment shows effect of hemorrhage alone
	11:35	13.0	18.4	0.71	5.15	−10	40	464	36.3	55–62			Period taken 5 minutes after bleeding 17 cc.
	12:15	14.4	19.8	0.71	5.65	−1	47	482	36.3	75–80			
	12:45	15.2	19.1	0.80	5.45	−5	46	536	36.4	82			
	1:45	15.0	20.2	0.74	5.69	−1	51	506	35.6	110			Blood pressure 50, 5 minutes before last observation. Period
	2:30	14.8	18.6	0.80	5.32	−7	40	637	35.8	65–85		52.0	taken 20 minutes after bleeding
Experiment XLIII, 5/15/19, 2600 grams	12:12	13.0	19.5	0.67	5.47		28	3402	37.1	130–120	11:30		Spontaneous drop of blood pressure
	12:40	10.9	16.6	0.66	4.66	−15	29	3080	37.0	95			
	1:5	11.8	17.1	0.69	4.80	−12	32	3364	37.0	85			1:30, Bled 10 cc. (pressure below 70 one hour). No trauma
	3:2	11.7	16.8	0.70	4.70	−13	29	4087	37.1	80			

Experiment XXXIII, 4/15/19, 3000 grams, ♂	10:50	18.4	25.3	0.73	7.10		38	440	35.9	115	9:35	43.5	
	11:37	16.5	19.1	0.86	5.55	−22	34	364	35.6	95			Bled at 11:15, 15 cc.
	12:34	17.8	23.1	0.77	6.56	−8	28	407	35.3	78–70			
	1:38	17.9	23.3	0.77	6.63	−7	32	469	36.0	82–84			Legs smashed 12:00–12:08
	2:3	18.1	23.0	0.77	6.68	−6	35	544	35.7	80–83			
	2:37	17.1	21.4	0.80	6.15	−13	36	559	35.9	80		43.5	
Experiment XXXV, 4/22/19, 2400 grams	12:0	14.4	22.0	0.66	6.16		30	482	36.7	105	11:0		Controls vary 14 per cent. Average taken
	12:20	14.7	18.5	0.80	5.28		25	461	36.6	90			
	12:45	14.2	16.7	0.85	4.85	−15	30	533	36.6	60–67		43.3	12:40, Bled 10 cc.
	1:47	14.4	15.4	0.94	4.56	−20	46	629	36.5	75			Effect of hemorrhage
	2:47	16.8	16.2	1.04	4.54	−21	46	1433	36.5	78–63			2:12, Both legs smashed. Traube-Hering waves developed at once
	3:48	10.6	13.1	0.81	3.76	−34	40	670	36.7	50		31.9	Cat died at 4:20 in profound shock

and at the time of observation the blood pressure was 95. It was, however, not rising. In experiment XXX, table 3, where blood pressure fell from 170 to 108 mm. Hg. after severe trauma, the metabolism still fell 14 per cent and 29 per cent; and in experiment XXXI, table 3, even though blood pressure after trauma was 85, the heat production was reduced −21 per cent and −24 per cent. The temperature in these last two experiments, however, was not satisfactory. Likewise in experiment XXXII, the metabolism fell 23 per cent even though the blood pressure was 100. In experiment XXXVI, table 4, fourth period, though the blood pressure was 80–75 in an animal rapidly developing shock, the metabolism was −26 per cent of the normal level. The explanation of these differences is obscure. After hemorrhage the blood pressure may be low for a time without marked drop in metabolism. After muscle injury the metabolism may be reduced before a great fall in blood pressure has occurred. Possibly the observations of Gesell (7) will satisfactorily account for these facts. He found that in the early stages of shock from tissue abuse there is usually a marked reduction of the "volume flow" of blood in peripheral organs, although blood pressure is only little changed, and he reports one instance of increased volume flow after hemorrhage though the blood pressure was falling. The *volume flow of blood* determines the oxygen delivery to the tissues, and this may vary to some degree without corresponding variation in blood pressure.

The reduction of blood pressure by increasing pericardial pressure, as described by Cannon (8), is due to mechanical venous obstruction, and is similar in its action to the methods described by Janeway and Jackson (9) and by Erlanger and Gasser (10). When the blood pressure is reduced by this procedure, the metabolism, as calculated from the respiratory gases, shows a marked prompt reduction to the level found with similar blood pressures in experimental shock (table 6). The respiratory quotient is also similar in that it rises. The prompt reduction of metabolism by this method of merely hindering the venous return to the heart is evidence that some mechanical factor such as retarded blood flow is the cause of the reduced metabolism. This is emphasized by the rapidity of the appearance of the reduction, which by this method seems to occur without delay.

The rapid appearance of diminished alkaline reserve in shock, as shown by the lowering of the blood CO_2 combining capacity, should not reduce metabolism but, if anything, should tend to raise it slightly, as shown by studies (11) in conditions where a similar drop in the reserve may occur.

A feature of the results is the rather low average respiratory quotient. In forty-seven observations in Raeder's publication (6) and in sixty-two normal observations in this series, the average respiratory quotient was the same—0.75. Wilenko (12) in ten periods with cats partly anesthetized by 1 gram urethane per kilo by mouth, had an average respiratory quotient of 0.79 in his controls. This rather low value, as also the work of Underhill (13), and the presence of a hyperglycemia (paper III), all suggest a decreased oxidation of carbohydrate under urethane anesthesia. This point will be more fully discussed in a future publication. Here it is sufficient to say that the control experiments demonstrate that the height of the basal metabolism remains constant under urethane for 4½ hours. Inasmuch as we are dealing with relative changes in each animal, the low respiratory quotient in the control periods does not affect the eventual conclusions. The tendency as shock develops has been for the respiratory quotients to rise—the average for twenty-one observations being 0.81, an effect, probably, of increased ventilation and the resulting pumping out of CO_2.

Having the animal anesthetized makes the determination of the basal metabolism a great deal simpler, for voluntary movements and emotional excitement are removed as factors which might raise the metabolism. The abnormality of some of the respiratory quotients reported here could practically all be traced to irregularities in breathing just prior to or during the observation. A period of hyperpnea previous to the observation gave a low respiratory quotient, and with hyperpnea during the period, the respiratory quotient was always elevated. In cats the breathing under urethane is apt to vary in quantity rather markedly and, as a result, no great stress may be laid upon respiratory quotients. Then, too, there is the factor of rapidly decreasing alkaline reserve with the marked fall of blood pressure, as shown by Cannon (14), and whether this is due to an accumulation of lactic acid or to a disappearance of alkali into the tissues, the effect would probably be a temporary pumping out of extra CO_2 into the expired air. The effect of this change in balance might well affect the dissociation curves of hemoglobin for oxygen and for CO_2 (15). With the low blood pressure found in shock, the effect on the exchange of substances between blood and tissue fluids may be considerably disturbed, and these factors might distort the relationship between the O_2 absorbed and the CO_2 given off in the lungs. As a result, little stress may be laid on the respiratory quotients obtained, because of the

TABLE 3

Respiratory metabolism in shock; mild shock

EXPERIMENT NUMBER, WEIGHT, DATE	TIME OF PERIOD	RESPIRATORY EXCHANGE PER MINUTE		RESPIRATORY QUOTIENT	CALCULATED CALORIES PER HOUR		RESPIRATORY RATE PER MINUTE	RESPIRATORY VOLUME PER MINUTE	RECTAL TEMPERATURE	BLOOD PRESSURE	TIME OF ANESTHETIZATION	REMARKS
		CO_2	O_2		Calories	Variation						
		cc.	*cc.*			*per cent*		*cc.*	*°C.*	*mm. Hg.*		
Experiment XXVIII, 4/2/19, 3100 grams	12:30	23.3	27.1	0.86	7.87		56	857	37.4	100–90	11:00	
	1:00	21.3	25.0	0.85	7.25		78	762	37.2	85		One leg crushed at 1:10 mildly
	2:30	19.6	26.9	0.73	7.61	+1	166	1287	38.2	80		Cat overheated
	3:50	16.5	24.0	0.69	6.72	−10	145–90	874	37.3	75		No severe shock developed
Experiment XXX, 4/7/19, 4000 grams, ♂	11:15	28.5	37.4	0.76	10.59		175	1823	37.5	165	10:10	
	11:40	31.0	39.4	0.79	11.23	+6	195	2400	37.3	150		11:30, Bled 15 cc.
	12:12	27.6	33.8	0.82	9.38	−14	146	2046	36.9	150		12:00, Both legs smashed
	2:00	24.7	32.6	0.76	9.33	−14	116	1504	36.9	112		1:40, Both legs resmashed
	2:50	22.2	26.9	0.83	7.74	−29	80	1120	36.5	108		No real shock developed
Experiment XXXI, 4/10/19, 3300 grams	10:33	20.8	24.9	0.84	7.20		22	509	36.5	150	9:42	Regulation of temperature bad
	11:20	18.6	22.6	0.83	6.51		28	475	36.5	95–100		Legs smashed 11:47 and 12:13
	11:55	17.3	22.0	0.79	6.29	−8	37	484	36.0	85–100		
	12:54	16.3	20.2	0.81	5.78	−15	34	476	35.4	70–65		Suggestive of shock
	1:45	15.3	18.7	0.82	5.44	−21	43	462	35.1	85		Recovering spontaneously
	2:27	13.7	18.5	0.75	5.21	−24	45	568	35.7	85		Temperature low
	3:22	15.6	18.3	0.85	5.30	−23	52	725	36.0	76		

Experiment XXXII, 4/12/19, 2700 grams	12:24	15.2	22.6	0.68	6.33		22	408	36.3	135	11:15	
	12:44	19.0	24.5	0.78	6.96	+10	22	496	36.2	135		1:07, Right leg smashed
	1:17	16.8	22.5	0.75	6.36	−4	15	386	36.2	130		1:40 and 2:12, Left leg smashed
	3:02	16.4	17.2	0.95	5.13	−23	32	627	36.2	100		No shock pressure but metabolism fell
Experiment XXXIX, 5/5/19, 2800 grams, ♂	11:35	17.2	23.5	0.73	6.61		29	424	37.5	135	10:45	
	11:55	16.1	22.5	0.72	6.30	−5	27	389	37.4	120		12:22, Bled 9 cc. Blood pressure fell to 80; rose rapidly
	12:45	16.1	21.5	0.75	6.07	−6	19	467	37.9	100–95		
	1:53	15.3	19.8	0.77	5.61	−13	28	547	37.4	80–87		1:05, Both legs smashed; shock just developing
Experiment LVII, 12/10/19, 4600 grams, ♀	12:05	22.3	31.0	0.72	8.70		18	613	38.9	128	10:30	
	12:25	21.6	30.9	0.70	8.67		20	608	38.8	120		1:10, Left leg smashed
	2:48	22.1	27.5	0.80	7.87	−9		950	38.3	73		Very mild shock
	3:11	21.1	24.5	0.86	7.11	−18	29	1241	38.6	72		Blood pressure never below 70

TABLE 4

Respiratory metabolism; severe shock

EXPERIMENT NUMBER, WEIGHT, DATE	TIME OF PERIOD	RESPIRATORY EXCHANGE PER MINUTE		RESPIRATORY QUOTIENT	CALCULATED CALORIES PER HOUR		RESPIRATORY RATE PER MINUTE	RESPIRATORY VOLUME PER MINUTE	RECTAL TEMPERATURE	BLOOD PRESSURE	TIME OF ANESTHETIZATION	BLOOD CO_2 COMBINING POWER	REMARKS
		CO_2	O_2		Calories	Variation							
		cc.	*cc.*			*per cent*		*cc.*	*°C.*	*mm. Hg.*			
Experiment XXXVI, 4/26/19, 2400 grams	11:48	11.1	15.8	0.70	4.44		40	391	37.1	135	10:45		Bled 8 cc. at 12:55
	12:20	10.6	15.6	0.68	4.38		36	369	36.8	100–130			Both legs smashed 1:00–1:05
	1:45	11.1	14.4	0.77	4.10	−7	34	408	37.3	75			
	2:45	9.4	11.4	0.82	3.23	−26	36	409	36.9	80–75			Traube-Hering waves
	3:30	8.2	11.3	0.73	3.28	−26	30	292	36.9	60–63			Traube-Hering waves
	4:08	4.0	6.1	0.65	1.71	−61	19–13	1162	36.7	55–40			Cat died 4:19 as period ended
Experiment XXXVII, 4/28/19, 3600 grams, ♂	1:10	19.8	26.5	0.75	7.48		28	470	36.5	152–140	12 N		1:55, Bled 10 cc. without loss of blood pressure
	1:30	22.2	28.3	0.78	8.06	+8	32	493	36.6	110–120			
	2:00	21.6	28.9	0.75	8.16	+5	27	546	37.0	130		41.4	2:25–3:25, Smashed both legs
	3:35	21.1	25.7	0.82	7.39	−5	26	594	37.5	110			
	5:50	15.6	18.5	0.84	5.35	−31	25	464	36.5	67–60		27.1	Profound shock just developing. 6:20, Cat died
Experiment XXXVIII, 5/1/19, 2400 grams	11:45	13.4	17.7	0.76	5.00		30–26	362	36.2	140	11:00		
	12:17	13.5	18.0	0.75	5.08		28–50	377	36.3	100			1:00, Bled 8 cc.
	1:12	11.5	16.5	0.70	4.63	−8	30	400	36.2	80			1:35 and 1:55, Both legs smashed. Shock developing
	2:22	16.4	20.2	0.81	5.80	+15	72–66	1212	36.4	80			
	3:25	10.4	12.5	0.83	3.61	−28	46	720	35.6	65			Shock
	3:45	7.1	9.8	0.73	2.74	−46	22	377	35.7	60			

Experiment XLIV, 5/17/19, 2800 grams, ♂	12:20	19.2	24.6	0.78	7.00		26	3857	37.4	120	11:25	Bled 9 cc. at 12:00 and blood replaced
	1:25	20.9	24.9	0.84	7.21		30	3861	37.4	100		
	1:45	22.7	26.4	0.86	7.67		32	4273	37.5	90		Legs smashed at 2:03
	2:45	23.2	23.7	0.98	7.09		29	6431	36.5	75		Severe shock since 3:00
	3:33	14.1	16.7	0.85	4.82	−34	34–30	4590	37.4	65–60		
Experiment LVI, 12/5/19, 4300 grams, ♂	11:41	23.2	32.0	0.73	8.98			959	38.7	126	10:15	12:45, Bled and transfused. 12:50, Leg smashed
	12:02	24.9	32.0	0.78	9.06			856	38.3	140–132		
	3:19	31.4	30.3	1.03	9.06	0		3295	38.3	75–70		Extreme hyperpnea
	3:36	24.5	24.3	1.01	7.26	−20		3628	38.3	64–59		Extreme hyperpnea

TABLE 5

Respiratory metabolism; shock and transfusions

EXPERIMENT NUMBER, WEIGHT, DATE	TIME OF PERIOD	RESPIRATORY EXCHANGE PER MINUTE		RESPIRATORY QUOTIENT	CALCULATED CALORIES PER HOUR		RESPIRATORY RATE PER MINUTE	RESPIRATORY VOLUME PER MINUTE	RECTAL TEMPERATURE	BLOOD PRESSURE	TIME OF ANESTHETIZATION	REMARKS
		CO_2	O_2		Calories	Variation						
		cc.	*cc.*			*per cent*		*cc.*	*°C.*	*mm. Hg.*		
Experiment XLI, 5/8/19, 3200 grams, ♂	11:50	15.9	23.1	0.69	6.47		*	599	36.3	145	10:50	Respiration rapid-irregular
	12:15	18.6	25.7	0.72	7.21		114–78	956	36.1	110		Respiration rapid and shallow. 12:55, Bled 10 cc.
	2:55	20.9	26.2	0.80	7.50	+7	78–86	1186	36.3	95		1:10–15, Both legs smashed
	3:30	12.2	18.0	0.68	5.04	−28	50–48	775	35.6	50–63		3:28, 4 cc. blood from right femoral vein. Shock developed at 3:30
	3:45	15.0	20.3	0.74	5.73	−18	41	1365	36.2	67		
	4:30	13.3	16.1	0.83	4.64	−33	27	797	35.4	105		Transfused with 20 cc. blood and 15 cc. mammalian Ringer 4:00. Temperature low. Traube-Herring waves
	4:45	12.9	19.3	0.67	5.40	−23	38–34	727	35.3	80–95		
Experiment XLVII, 7/17/19, 2600 grams, ♀	1:22	17.2	22.0	0.78	6.27		51	571	37.1	92	11:00	Legs smashed at 2:40
	2:20	14.6	21.6	0.67	6.07		63	660	36.7	105		No shock yet
	3:43	14.8	21.6	0.69	6.06	−2	64	692	36.3	82		Shock developing rapidly
	4:05	16.1	17.7	0.91	5.20	−16	83	967	36.4	75–65		
	4:17	12.3	15.7	0.78	4.47	−28	72–176	944	36.2	50–70		
	4:48	13.5	17.7	0.75	4.98	−19	40	493	35.2	95–105		4:25–40, 70 cc. blood transfused. Low temperature unexplained except by transfusion
	5:19	12.7	21.0	0.61	5.88	−5	46	476	36.3	110		
	5:38	14.1	19.7	0.72	5.53	−10	42	482	36.5	105		

Experiment XLVIII, 7/22/19, 2700 grams, ♂	11:45	11.8	18.0	0.66	5.04		37	366	36.3	108	10:20	Normal
	12:12	13.7	18.4	0.74	5.18		36	363	36.2	95		
	12:35	14.8	18.1	0.82	5.20		35	391	36.0	105		
	2:25	11.4	14.5	0.79	4.13	−20	27	395	36.3	60		Onset of true shock level
	2:49	11.8	13.9	0.85	4.03	−22	26–64	550	36.3	65		Respiration increasing rapidly
	3:30	17.2	22.3	0.77	6.34	+23	30	424	36.2	130		3:03–15, 65 cc. blood transfused
	4:02						40	426	36.2	115		Analyses discarded
	4:35	12.7	18.6	0.68	5.23	+2	40	524	36.2	100–115		
Experiment LIII, 11/24/19, 4400 grams, ♂	11:40	23.4	31.8	0.73	8.97			941	38.4	112	10:50	
	12:23	21.7	30.8	0.71	8.63		56	1069	38.3	110		12:55–1:20, Bled, transfused and legs smashed
	2:50	28.1	36.1	0.78	10.28	+17	+	2866	38.3	66		
	3:00	26.8	36.6	0.75	10.35	+18	†	3330	38.4	62		Shock
	3:24	22.2	31.3	0.71	8.77	0	39	901	38.6	116		3:08–17, Bled 15 cc. Transfused 101 cc.
	3:35	20.1	30.8	0.65	8.63	−2	36	927	38.5	124–136		
Experiment LII A, 11/4/19, 4200 grams	11:41	18.6	26.5	0.70	7.43		18	447	36.8	130	10:35	
	12:07											
	12:27	17.7	21.4	0.83	6.17	−17		441	36.8	98		2:00–07, Left leg smashed
	2:50	16.1	19.6	0.82	5.65	−24	16	411	36.9	80		2:50, Cat going into shock
	3:03	17.5	19.3	0.91	5.67	−24	14	463	36.8	74		Cat in shock
	4:01	17.9	20.4	0.88	5.95	−20		327	36.4	100		3:45, 67 cc. blood transfused after bleeding 20 cc.
	4:27	16.1	21.8	0.74	6.15	−17		517	36.6	118		Cat has recovered from shock

* Irregular.

† Intense dyspnea.

TABLE 6

Respiratory metabolism in shock; pericardial pressure

EXPERIMENT NUMBER, WEIGHT, DATE	TIME OF PERIOD	RESPIRATORY EXCHANGE PER MINUTE		RESPIRATORY QUOTIENT	CALCULATED CALORIES PER HOUR		RESPIRATORY RATE PER MINUTE	RESPIRATORY VOLUME PER MINUTE	RECTAL TEMPERATURE	BLOOD PRESSURE	TIME OF ANESTHETIZATION	BLOOD CO_2 COMBINING POWER	REMARKS
		CO_2	O_2		Calories	Variation							
		cc.	*cc.*			*per cent*		*cc.*	*°C.*	*mm. Hg.*			
Experiment III, 10/5/18, 2900 grams, ♀	10:48	12.5	17.0	0.74	4.77		25	406	34.5	145–150	9:15		
	12:11	10.5	11.0	0.96	3.30	−31	varied		35.4	60			12:08, Blood pressure reduced by pericardial pressure
	2:12	10.2	12.5	0.81	3.60	−25	32	527	34.0	60			
Experiment VI, 10/11/18, 7000 grams, ♀ Dog	10:36	57.7	65.8	0.88	19.21		43	2190	34.0	120		50	
	11:13	35.8	38.9	0.92	11.48	−41	46	2060	34.5	60		43	11:10, Blood pressure reduced by pericardial tension
	12:24	41.7	41.2	1.01	12.30	−36	52	2710	34.5	60		37	
	2:23	33.6	30.6	1.10	9.15	−52	48	2950	32.7	60		34	Temperature of dog low
Experiment VII, 10/12/18, 12,930 grams, ♀ Dog	11:07	58.4	77.5	0.77	21.91		46	2280	35.2	120		47	
	11:46	57.8	70.1	0.82	20.19	−8	68	3560	35.2	100		43	Blood pressure reduced gradually by increasing pericardial tension
	12:27	47.8	51.5	0.93	15.22	−31	51	3300	34.8	80		36	
	12:42	38.1	40.9	0.93	12.11	−45	45	3080	34.3	60		30	
	1:20	44.1	45.1	0.98	13.50	−38	33	2450	32.3	80		32	Very low temperature
Experiment XLV, 7/2/19, 2800 grams, ♂	1:06	17.2	24.4	0.71	6.84		64	632	37.0	95	10:30		Variation of 6 per cent. Average taken
	1:40	16.1	23.0	0.70	6.45		62	644	37.4	90			
	2:05	13.2	17.1	0.77	4.86	−27	59	516	37.5	45–55			Taken immediately after increased pericardial pressure
													2:46, Cat died

Experiment XLIX, 7/25/19, 2500 grams, ♂	3:34	8.6	13.8	0.62	3.89		43	252	36.2	90	11:15	Cannula in pericardium
	3:58	10.3	13.9	0.74	3.90		46	258	36.4	93		4:24, Intrapericardial pressure increased by gum-salt solution
	4:25	9.5	11.7	0.81	3.37	−13	38	285	36.5	55		
	4:44	9.0	10.6	0.85	3.07	−21	40	278	36.6	58		
	5:03	8.8	10.6	0.83	3.06	−21	42	296	36.8	59		Cat killed
Experiment LIV, 12/11/19, 3300 grams, ♂	12:00	16.3	23.8	0.69	6.67			478	38.0	142–116	10:20	A control experiment to show recovery after a low blood pressure
	12:19	17.8	24.3	0.73	6.82			544	38.0	108		
	2:14	17.2	23.2	0.74	6.55	−3	32	516	38.3	112		At 1:11, Blood pressure reduced to 60. At 2:10, pericardial pressure removed
	2:37	16.4	21.4	0.77	6.06	−10		549	38.3	110		

extremely complicating factors which may be influencing them. However, the oxygen absorption from the lungs must represent the amount of oxygen available for metabolic uses in the tissues, inasmuch as the blood leaves the heart normally saturated with oxygen (16). That this absorbed oxygen represents the amount used by the body seems highly probable, as otherwise there would be an accumulation of oxygen in the tissues, a condition which seems decidedly unlikely. In all these observations, therefore, the oxygen absorption has been used as the basis of comparison, and the CO_2 assumes a relatively unimportant rôle through its influence on the respiratory quotient.

The reduced metabolism affords an explanation for the marked reduction of body temperature in shock, which may go as low as 87.8°, or even 76.1° in cervical spine lesions, according to Weil (18) and to Volkmann (17). This investigation, however, does not indicate that the reduction is usually a forerunner of the onset of shock, or that it is a causative factor in the production. In fact, in two experiments the metabolism just before the onset of shock was slightly elevated above the normal level.

The volume of respiration per minute has likewise been studied. The average ventilation per minute of the control observations was 557 cc. in twenty-one experiments; the average after crushing the muscles and before the onset of a shock blood pressure level was 860 cc. in ten experiments, (a variation of +54 per cent from the control observations), and after the onset of shock it was 635 cc. in thirteen experiments. This variation is hardly enough to account for the onset of shock, in these muscle trauma experiments, by the acapnia theory advanced by Henderson and Haggard (19), (20). Besides, rapid breathing with a higher ventilation rate per minute than in shock has been repeatedly seen under urethane anesthesia without the onset of spontaneous shock. These data also show that the fall of the metabolic rate was not due to changes in either the volume or exertion involved in respiration.

With the metabolism so much reduced by shock, it naturally became of interest to know the effect of transfusion of a sufficient amount of blood to bring about recovery. Table 5 shows five such experiments in three of which the metabolism returned to normal limits, while in experiment XLI the metabolism remained low. In experiment XLVIII, the figures for the first period after transfusion were above the normal determinations. Experiment LIV in table 6 shows the effect of reducing the pressure to shock level by pericardial pressure.

Periods III and IV were taken directly after releasing the pressure, and showed a normal rate. It therefore seems that making the circulation adequate causes the low metabolism of shock to disappear promptly.

CONCLUSIONS

1. Ethyl carbamate (urethane) is a satisfactory anesthetic for the study of gaseous metabolism in animals over short periods of time.

2. Experimental traumatic shock causes a marked fall in the rate of basal metabolism to 70 per cent of the original level. The degree of fall is dependent upon the severity of the shock produced.

3. A similar fall of the metabolic rate may be rapidly accomplished by interfering with the circulation by increased pericardial pressure.

4. The effect of hemorrhage is not constant. It may temporarily lower, or have no immediate effect on the metabolic rate.

5. Recovery from shock after blood transfusion is usually associated with a prompt return of the metabolic rate to a normal level.

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STUDIES IN EXPERIMENTAL TRAUMATIC SHOCK

II. The Oxygen Content of the Blood

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In studying the basal metabolism of experimental traumatic shock it became clear that the reduction of the calories utilized was dependent upon some undetermined factor. This was suggested by the fact that the fall in metabolic rate did not always coincide with the fall in blood pressure. Other observers have noted that there were marked changes in the circulation before a shock level of blood pressure was approached. Gesell (1) showed a slowing of blood flow through the salivary gland before a fall in pressure had developed. Yandell Henderson, (2) while working with shock induced by intestinal trauma in dogs, found a markedly decreased O_2 content in the venous blood, which he thought followed the failure of the venopressor mechanism and demonstrated a true anoxemia.

These observations suggested that the determination of the oxygen of the arterial and venous blood, as well as the blood flow during the development and recovery from traumatic shock, might give evidence as to the cause of the fall of metabolism (3).

Method. The animals used were cats, and the methods used for inducing traumatic shock and determining metabolism were similar in all respects to those previously described (3). The values for blood oxygen were obtained by the methods of Van Slyke (4).

The blood was withdrawn in two ways: *a*, by inserting a needle in a branch of the femoral artery and vein, and so entering the larger vessels without causing any stasis; *b*, the more satisfactory way, by inserting thin catheters down the right carotid artery and right superficial jugular vein until they reached the heart. The blood was collected in glass syringes, under paraffine oil, and put into tubes under oil (5).

[1] This is study no. X of a series on the physiology and pathology of the blood from the Harvard Medical School and allied hospitals.

By this method blood could easily be obtained without exposure to air. In order not to disturb the blood volume in the experimental animal, the amount removed for analysis was promptly replaced by an equal amount of citrated cat's blood. Thus fairly large samples of arterial and venous blood could be obtained without permanently affecting the blood pressure or blood volume.

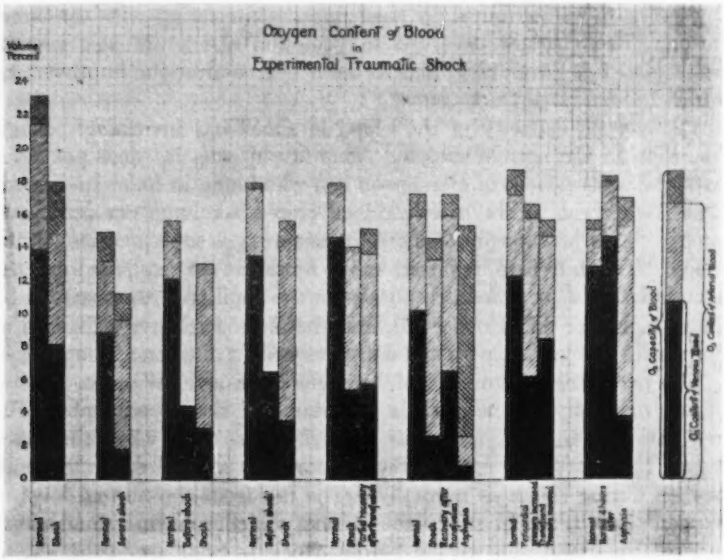

Fig. 1. Normal = Animal under urethane anesthesia.
Before shock = After muscle trauma, but before a true shock level of blood pressure had been established.
Asphyxia = Clamping off trachea completely for 4 or 5 minutes.

After shock had been established for about 30 minutes, as shown by a fall of blood pressure to 60–70 mm. Hg., the blood samples were taken and were immediately followed by a large transfusion of blood, as much as 100 cc. being given in an attempt to relieve the shock. In one case this accomplished a permanent recovery of blood pressure to its original level. In cases where a few minutes' delay followed the taking of the blood samples from the shocked animals, only slight recovery of blood pressure followed the transfusion.

Discussion. Figure 1 shows graphically the more important changes which occur in the oxygen of the blood in traumatic shock. The most striking effect is seen in the oxygen content of the venous blood, which falls very markedly in shock—not only in actual content of oxygen but in percentage of saturation.[2] This is well shown in all the experiments in table 2, but possibly most notably in experiments LIII and LV, and is also present in a control experiment LIV, table 1, where a low pressure was obtained by mechanically interfering with the circulation. The changes observed in profound shock are also present as the shock is developing, and to lesser degree after the improvement which follows large transfusions.

The oxygen capacity of the blood in shock has invariably become less than in the normal sample. This fall in capacity does not agree with the observations of Henderson (2), who found in four experiments that the oxygen of the arterial blood rose 1.5 volume per cent after shock. This he interpreted as demonstrating a concentration of the blood. The fall here reported may, however, be explained by the accumulation of red blood corpuscles in the capillaries, as observed by Cannon, Fraser and Hooper (6), and therefore a relative reduction of corpuscles in venous blood, and not necessarily a dilution of the plasma.

The percentage saturation of hemoglobin in arterial blood has not varied markedly in the various conditions of the experiments. The ventilation is at least adequate throughout, so that when the blood leaves the heart and reaches the tissues it is as well saturated with oxygen during shock as normally. The fall from the normal level of oxygen takes place in the venous blood, which confirms Henderson's observations, and this occurs before shock as well as during shock. In experiment LVI, while the blood pressure was, and had been, 104–94 mm. Hg. for 1½ hours after the muscle injury, the oxygen content of the venous blood had fallen from 12.27 to 4.55 volumes per cent. So also in experiment LVII, although the blood pressure was 84 mm. Hg. after the muscle injury, the oxygen content of the venous blood had fallen from 13.68 to 6.64 volumes per cent.

A similar, though less marked, decrease in the oxygen content of the venous blood is seen after recovery by transfusion as seen in experiment LIII, table 2. That this is sufficient to indicate a true asphyxia in the tissues cannot now be proved because the head of oxygen pressure necessary for normal oxidation is not yet definitely known. How-

[2] The percentage of saturation as used in this paper, represents the oxygen content of venous blood divided by the oxygen capacity of the arterial blood.

ever, the very small amount of oxygen present (with the attendant low partial pressure) makes a true anoxemia possible.

It is true, however, that the venous blood may be as low in oxygen in severe anemia as it is in shock, but in this condition the oxygen of the arterial blood is likewise reduced. Morawitz and Rohmer (7) found that in three human cases of very severe anemia, where the oxygen-carrying capacity of the blood was 4.5 per cent or less, the venous blood had an oxygen content as low as 0.67 per cent, and they assumed an increased blood flow to explain the normal metabolism which is still found in these cases. Lundsgaard (8), also studying patients with anemia, found the venous blood contained as low as 1.16 volume per cent of O_2 in a case with an oxygen-carrying capacity of 5.93 per cent. He concludes that the tissues extract oxygen from the blood with equal readiness whether there is a large oxygen reserve in the blood, "or practically no reserve, as in anemia." These cases, however, had very low oxygen capacities, and therefore the low O_2 content of the venous blood meant a less complete dissociation[3] of hemoglobin and O_2 than would a similar figure in a normal blood. It is the amount (percentage) of this dissociation which must influence the partial pressure of the dissolved oxygen, and this latter is the important factor in the migration of oxygen into the tissues. The oxygen content of normal blood may, therefore, be three or four times that of anemic under the same partial pressure of O_2. As a result, under similar conditions, one would expect to find a much larger figure for the total venous content of oxygen in these shock experiments than would be found in anemia, because anemic blood has less hemoglobin. In fact, the *percentage* saturation of the venous blood in these anemia cases, (16 per cent and 20 per cent), is about the same as in the cases of severe shock, in spite of the lower venous *content*.

A more direct control of the value of the oxygen content found in these experiments are the figures obtained in animals after 4 or 5 minutes of complete asphyxia, for here, just before death, the oxygen value of the venous blood was not very much lower than that found in shock. This is of course indirect evidence, for the matter of greatest importance to the tissue is the oxygen content of the arterial blood. Still, the oxygen content of the venous blood must give a satisfactory

[3] This dissociation is approximately represented by the "per cent of saturation" column in tables 1 and 2. It is approximate, because the small amount of oxygen dissolved in the plasma would be about the same in anemic and normal bloods.

indication of conditions in the venous end of the capillaries, and in the asphyxia experiments must surely indicate an oxygen content which is entirely inadequate for the use of the tissues.

The explanation of this marked anoxemia lies most probably in a slowed blood flow which has been demonstrated in shock, and which can be very well demonstrated in these experiments by the method used by Means and Newburgh (9). In brief it is based on the formula:

$$\text{Volume output of heart per min.} = \frac{\text{cc. } O_2 \text{ absorbed through lungs}}{\text{Volume per cent oxygen utilization of blood}}$$

Using this formula we can calculate the blood flow of several of our cases. The results are shown in tables 1 and 2. It is clear that the blood flow becomes markedly slowed before the onset of a shock level of blood pressure, and that this slowing precedes the fall in metabolism, demonstrated in paper I.[4] This is demonstrated in experiments LVI and LVII. It may therefore be assumed that the fall in metabolism is a secondary manifestation of the decreased blood flow, and of the markedly reduced oxygen content of the venous blood, and is probably due to a true anoxemia. This suggestion is further borne out by the similar findings following increased pericardial tension (exper. LIV), for this must suddenly decrease the rapidity of blood flow. There is a much increased oxygen utilization in the blood and there is also a very prompt fall in the level of the basal metabolism (3), although the only disturbing factor is in the circulation, and no toxic effect from tissue injury can be involved. Verzar (10) has also shown that when perfused muscles are given inadequate oxygen supply the height of their metabolism falls.

Under these conditions we may add another factor to the vicious cycles described by Cannon (11). Krogh (12) has shown that as an oxygen want develops in contracting muscles, many empty capillaries fill with blood, a change which reduces the distance necessary for the diffusion of gases into the tissues. Thus, as anoxemia develops, the capillary bed would increase in volume. This would further decrease the already slowed blood flow, and the slower the flow the greater would probably become the oxygen consumption per cubic centimeter of blood, and hence the decrease in oxygen of venous blood.

[4] Experiment LIII does not show so striking a drop as the other two. It was abnormal, however, in being the only observation which showed a rise in metabolism during shock, instead of a fall. This was probably due to the intense dyspnea.

TABLE 1

Normal controls

NUMBER, WEIGHT, DATE	TIME OF SAMPLE	O_2 OF ARTERIAL BLOOD		O_2 OF VENOUS BLOOD			HEMOGLOBIN CALCULATED	CO_2 COMBINING POWER	BLOOD PRESSURE	METABOLIC RATE O_2 ABSORBED PER MINUTE	BLOOD FLOW PER MINUTE	REMARKS
		Capacity	Content	Content	Consumption	Saturation						
		vol. per cent	*vol. per cent*	*vol. per cent*	*vol. per cent*	*per cent*	*per cent*	*vol. per cent*	*mm. Hg.*	*cc.*		
LIX	11:57	15.93	15.38	13.12	2.26	82.4	86.1		92	24.9	1103	Transfused 30 cc. after bleeding
3.5 kgm.	4:07	18.68	18.35	14.93	3.42	79.9	100.7		110	21.5*	630	Transfused 45 cc.
12/12/19	4:24	17.33		3.89		22.4			50			After 4 minutes asphyxia
LXIX	12:55	15.7	16.41	11.80	4.61	75.2	83.6		110	21.6	469	
2.7 kgm.	4:35	15.0	16.38	9.50	6.88	63.3	82.4		108	19.5	284	
5/27/20												
LVIII	2:10	20.92	19.67	14.30	5.37	68.4	113.0		100	20.5	383	
2.9 kgm.	4:35	21.87	17.88	13.47	4.41	61.6	117.0		120	23.8	539	
4/27/20												
LXII	2:45	17.5?	18.0	9.90	8.1	55.0	89.0		100	23.2	283	
2.6 kgm.	5:00	18.4	18.0	9.10	8.9	49.5	93.0		155	22.9	253	
5/14/20												
LIV	12:47	18.96	17.45	12.50	4.95	65.9	102.0	57.4	112	24.0	485	Normal
3.3 kgm.	1:50	16.9	16.07	6.37	9.70	37.7	91.0	46.8	60			Blood pressure reduced by pericardial pressure for 45 minutes
12/1/19	2:50	15.92	14.92	8.69	6.23	54.6	86.0	47.7	105	22.3	358	Normal for 35 minutes

* Five and one-half hours after anesthesia.

TABLE 2

Experimental traumatic shock

NUMBER, WEIGHT, DATE	TIME OF SAMPLE	O_2 OF ARTERIAL BLOOD		O_2 OF VENOUS BLOOD			HEMOGLOBIN CALCULATED	CO_2 COMBINING POWER	BLOOD PRESSURE	METABOLIC RATE O_2 ABSORBED PER MINUTE	BLOOD FLOW PER MINUTE	REMARKS
		Capacity	Content	Content	Consumption	Saturation						
		vol. per cent	*vol. per cent*	*vol. per cent*	*vol. per cent*	*per cent*	*per cent*	*vol. per cent*	*mm. Hg.*	*cc.*		
LI	2:35	17.3	18.1	14.8	3.3	85.6	95.0	36.0	124			Normal
4.1 kgm.	4:20	13.9	14.2	5.5	8.7	39.6	75.4	34.1	56			Mild shock for 1 hour
10/22/19	5:00	15.3	13.8	5.9	7.9	38.5	82.7	40.6	81			After transfusion 43 cc. blood
LII	3:30	23.3	21.6	14.0	7.6	60.2	120.3	40.2	143			Normal
4.9 kgm.	6:05	18.1	14.2	8.3	9.8*	45.9	98.0	37.1	68			Shock for 1 hour
10/29/19												
	12:55	17.46	16.16	10.32	5.84	59.1	94.5	40.4	120	31.3	536	Normal
LIII	3:08	14.76	13.46	2.69	10.77	18.2	79.8	33.8	62	36.4	337	Shock for 30 minutes
4.4 kgm.	4:29	17.46	16.17	6.73	9.44	38.5	94.5	40.4	125	31.0	328	Recovery after transfusion of 100 cc. blood
11/24/19	4:34	15.59	2.69	0.89	1.8	5.7	89.6	43.3	70			Asphyxia 3 minutes by clamping trachea
LV	12:55	15.02	13.30	8.99	4.31	59.9	81.1	41.9	80			Normal. Transfused 27 cc.
3.1 kgm.	2:35	11.32	9.73	1.87	7.86	16.5	61.1	25.6	44			Very severe shock for 30 minutes
12/4/19												
LVI	12:35	15.77	14.54	12.27	2.27	77.8	85.1	48.2	132	32.0	1390	Normal
4.3 kgm.	3:02			4.55	7.70†				94	30.3	400†	Before shock developed
12/5/19	4:00	13.16	Clotted	3.18	9.98†	24.2	69.4	45.4	52	24.3	272	Severe shock
LVII	12:47	18.09	17.78	13.68	4.10	75.6	97.8		120	31.0	756	Normal
4.6 kgm.	1:58			6.64					84	27.5	308†	Before shock developed
12/10/19	3:25	15.81		3.65	12.16†	23.1	85.5	39.3	70	24.5	206	Mild shock

* Animal stopped breathing just before taking sample.

† Capacity substituted for oxygen content. These figures therefore approximate.

CONCLUSIONS

1. There is a markedly diminished oxygen content of the venous blood in experimental traumatic shock. This change occurs before the blood pressure falls to a shock level, and is still present after apparent recovery from shock.

2. The blood flow is also greatly decreased in the development of, during and after shock.

3. The resulting anoxemia of the tissues may be the cause of the decreased metabolism.

4. The sequence of these events in traumatic shock is discussed.

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STUDIES IN EXPERIMENTAL TRAUMATIC SHOCK

III. Chemical Changes in the Blood

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In experimental traumatic shock there is a marked decrease in the rate of blood flow and of general metabolism. Decreased blood flow and blood pressure result in a diminished secretion by the kidney (1). It is of interest to know what are the effects of such acute abnormal conditions upon the chemical constituents of blood, especially as a chemical cause of shock is now being seriously considered.

Some work in this field has been done by French investigators. Duval and Grigaut (2) studied the non-protein nitrogen of the blood in shock and concluded from their results that in the war-wounded there was an increase in the non-protein nitrogen of the blood, which started promptly after the wounding, was at its height during the second day and then gradually returned to normal. This increase was slight in unshocked cases, whether the wounds were infected or not. The retention differed from that found in nephritis in that the nitrogen increase in blood occurred not markedly in the urea portion but in the remainder of the non-protein nitrogen.

Whipple and his collaborators (3) studied the blood in the intoxication following intestinal obstruction, and after injection of the toxic proteoses which developed in obstructed intestines or in closed intestinal loops. The response to these injections was one which in many ways resembled traumatic shock,—with a fall in temperature and blood pressure. The injection was followed by a large increase (40 per cent or more) in the non-protein nitrogen of the blood, but this increase was found chiefly in the blood urea nitrogen, although the amino- and peptid-nitrogen also showed slight increases.

It is thus seen that the conclusions of the French and of the American investigators are somewhat contradictory, though it may be conceded that the response obtained by proteose injection is not a true shock.

At any rate, neither of these investigators have found any chemical change in blood other than rise in non-protein nitrogen which may be regarded as characteristic of traumatic shock.

The method of analysis used in our experiments was that of Folin and Wu (4). The urea was always determined by means of urease and aeration, as hydrolysis with the autoclave would also decompose the urethane used as an anesthetic. The figures obtained by the latter method were 10 to 15 mgm. too high, and it may therefore be concluded that the blood in our experiments contained about this amount of urethane N per 100 cc. The urethane contributed but little to the non-protein nitrogen as actually determined. It is so volatile that most of it is expelled in the course of the digestion. Experiments with a pure urethane solution containing 10 to 15 mgm. N per liter (i.e., as much urethane N as the blood filtrate might contain) have shown that only 3 to 4 mgm. N were fixed by the acid digestion mixture. The values of the total non-protein N obtained are, therefore, only 3 to 4 mgm. higher than the actual total non-protein nitrogen minus urethane nitrogen.

The creatin N represents as usual the difference between the total creatinine and the preformed creatinine multiplied by 0.37. In the first few experiments both the total creatinine and the preformed creatinine were determined, but as the latter showed no appreciable variation during anesthesia,—averaging 2 mgm. creatinine per 100 cc. blood, in control as well as in shocked animals[1]—its separate determination was discontinued in later experiments in order to economize the blood filtrate. Its average value was used for the calculation of the creatin.

In tables 1 and 2 are shown the results of our experiments. It is clear that in the control experiments there was no marked rise in any of the chemical constituents studied. This is true even in the experiments where the blood pressure and the blood flow were reduced by mechanical means but without muscle trauma (exper. LIV). In the animals in shock, however, there was usually a marked increase of all the constituents which we determined, over what was present before

[1] In a control experiment, 1 hour and 10 minutes after anesthesia the blood contained 5.2 mgm. total creatinine and 2.1 preformed creatinine per 100 cc. blood. Five hours later the total creatinine was again 5.2 mgm. and the preformed creatinine was 1.8 mgm. In another experiment (2 hours after traumatization) the blood contained 15 mgm. total creatinine and only 2.3 mgm. preformed creatinine.

TABLE 1

Control experiments; blood analyses in untraumatized animals

EXPERIMENT NUMBER, DATE	TIME OF BLOOD SAMPLE	BLOOD PRESSURE	TIME OF BLOOD PRESSURE BELOW 80 MM. Hg.	BLOOD ANALYSES, MILLIGRAMS PER 100 CC. OF BLOOD					BASAL METABOLISM		REMARKS
				Total non-protein nitrogen	Urea		Creatin nitrogen	Sugar	Time	Calories per hour	
					Nitrogen	Per cent					
		mm. Hg.									
XXVII 3/31/19	12:49	158		48	26	54	1.2	282	——	——	Normal control
									1:28	7.34	
	5:10	141		47	30	64	1.2	280	4:30	7.19	
									5:30	6.84	
7/15/19	10:44	110		52	29	56	1.9	206	11:00	4.10	Normal control
									11:22	4.19	
	5:30	94		55	32	58	1.8	286	4:19	3.43	
									5:11	3.20	
11/18/19	11:34	114		52	28	54	1.4	276			Blood pressure reduced by intrapericardial pressure. No muscle trauma
	1:10	60	90	58	29	50	1.7	328			
LIV 12/1/19	12:40	114		48	26	54	1.2	310	12:15	6.75*	Blood pressure reduced by intrapericardial pressure
	1:45	65	40	47	28	60	1.2	324			Pericardial pressure removed. Cat transfused. Good recovery of original blood pressure
	2:00										
	2:50	116		50	28	56	1.1	282	2:25	6.31*	

11/19/19	11:16	146	20	58	29	50	1.3	320				Under ether anesthesia
	12:35	70		66	32	49	1.3	334				Under urethane for 1 hour 15 minutes
XXXIV 4/19/19	11:30	106		48	28	58	1.5	250	11:11		5.73	Hemorrhage alone. Blood pressure markedly reduced by taking blood sample. No trauma
									11:42		5.16	
	2:25	108		43	29	67	1.6	276	1.51		5.69	
									2.35		5.32	

* Average.

TABLE 2

Blood analyses after muscle trauma

EXPERIMENT NUMBER, DATE	TIME OF BLOOD SAMPLE	BLOOD PRESSURE	TIME OF BLOOD PRESSURE BELOW 80 MM. Hg.	BLOOD ANALYSES, MILLIGRAMS PER 100 CC. OF BLOOD					BASAL METABOLISM		REMARKS
				Total non-protein nitrogen	Urea		Creatin nitrogen	Sugar	Time	Calories per hour	
					Nitrogen	Per cent					
		mm. Hg.									
6/9/19	11:10	155		60	42	70	2.0	286			Cat severely traumatized but no true shock. Blood pressure never below 83
	1:40	93		53	34	64	2.2	400			
6/19/19	11:17	126		53	39	74	1.8	296			After trauma to both legs blood taken as cat seemed about to go into shock
	1:00	80		65	42	65	1.3	334			
6/14/19	11:26	158		55	32	58	2.0	222			Muscles severely traumatized. Marked drop in pressure but no true shock level
	2:40	85		57	37	65	3.0	258			
10/21/19	2:34	110		60	35	58	2.4	320			Severe muscle trauma at 3:00 with prompt drop of blood pressure below 80. Transfusion at 4:26 with only partial recovery (46 cc. blood)
	4:15	60	70	70	40	57	2.8	440			
	4:50	82		71	40	56	2.8	440			
XXXIII 4/15/19	11:15	115		55	35	64	1.3	196	10:50	7.10	Legs smashed at 12:08. Very mild shock and no marked drop in respiratory metabolism
									11:37	5.55	
	2:48	80	140	64	43	67	3.5	400	2:42	6.15	
XXXV 4/22/19	12:40	84		53	25	47	1.5	222	12:27	5.28	Marked reduction of blood pressure from hemorrhage alone. Legs smashed at 2:12 with prompt shock developing
									12:51	4.84	
	3:58	42	280	77	42	55	6.1	364	3:53	3.76	

XL 5/6/19	1:00	100	Few	53	25	47	1.9	242			Very sudden onset of shock after severe resmashing of muscles with prompt death
	3:20	60	mins.	52	28	54	3.7	392			
XXXVII 4/28/19	1:55	126		50	28	56	2.2	250	1:36	8.06	Legs smashed at 2:25 and 3:25. Severe shock
									2:06	8.16	
	6:20	52	80	70	42	60	5.7	400	6:02	5.35	
XXXVIII 5/1/19	1:00	80–100		51	35	67	2.2	296	12:24	5.08	Both legs smashed at 1:35 and 1:55. Severe shock
									1:17	4.63	
	3:55	62	70	74	49	66	6.0	400	3:55	2.74	
XXXIX 5/5/19	12:22	104		47	25	53	1.8	306	12:02	6.30	1:05. Both legs smashed. Mild shock
									12:51	6.07	
	2:40	74	90	59	33	48	4.5	550	1:59	5.61	
XLI 5/8/19	12:55	116		46	20	43	1.5	188	12:39	7.30	1:00. Both legs smashed. Shock developed on removing blood for analysis. Transfusion at 4:00 with 20 cc. blood. Sample IV is blood from femoral vein leaving traumatized muscle. Sample V is taken from carotid artery at same time
									3:00	7.50	
	3:28	84		50	23	46	4.2	250	3:35	5.04	
	Blood used for transfusion			51	29	57	2.2	276			
	5:00			49			4.8				
	5:00	80		50	24	48	3.7	333	4:49	5.40	
6/25/19	11:10	125		50	28	56	2.2	296			Blood CO_2 combining power 36.5 at 12:06. Rapidly developing very severe shock. After muscle trauma blood CO_2 combining power 22.3 volumes per cent
	2:15	70	20	57	32	56	3.2	400			

trauma. This increase was not marked in traumatized animals which did not go into shock,—and, in fact, the rise tended to run parallel with the severity of the shock.

The most significant result of the blood analysis is that in connection with the creatin. In control animals the creatin content of blood remained practically unchanged during the five hours of the experiment. In animals which were traumatized but had not gone into shock the blood creatin showed an unmistakable increase. When shock developed, the creatin figure rose frequently to three times the normal. The source of the increased creatin in blood is the injured muscle. This is not only in accord with the known facts but is also shown in experiment XLI. The blood from the femoral vein contained distinctly more creatin than did the carotid blood. According to the views of Folin and Denis (5), creatin does not exist as such in the intact muscle and it is a post-mortem product set free by the dying tissue. While these investigators based their view on indirect though convincing data, the results of our experiments seem to afford direct evidence.

The parallelism between blood creatin and the severity of the shock does not of course indicate that creatin itself is responsible for this condition. Creatin is innocuous even in large doses. Simultaneously with the liberation of creatin from the autolyzing muscle there is probably formed a large number of other nitrogenous substances—possibly histamine and the like, and to these substances may possibly be ascribed the cause of shock. The increased blood creatin is merely an index of the extent of the necrosis which the injured muscle has undergone. Since creatin is derived solely from the injured muscle, the results of our experiment seem to afford suggestive chemical evidence in support of the view already prevalent that the shock is produced by some substance coming from the injured muscle (6), (7).

Although an increase in the total non-protein nitrogen always attended the development of shock, the increase was slight except in cases where the shock was profound. This relatively slight increase of total nitrogen is an excellent check on the increase of creatin, for it shows that the accumulation is due to increased production and not simply to kidney inefficiency, which would probably cause a parallel rise of all constituents. We are inclined not to attach much significance to the variation of the total nitrogen (and the percentage of urea N) on account of the complication by the urethane, but our results agree rather well with those of Whipple and collaborators (3),

and it may be concluded that albumoses, as such, could not have played any important rôle in the development of shock.

Some work has been done on the blood sugar content in traumatic shock. Cannon (8) reported that there was surely a normal amount if not a slightly increased blood sugar in wound shock. Fabre, Wertheimer and Clogne (9), however, report a reduced blood sugar content in shock. In our control experiments the blood sugar, while always high on account of anesthesia, did not rise greatly in the second sample. In the traumatized cases, however, there was nearly always definite and marked rise in the sugar content of the blood. Too much stress may not be laid upon the extent of the rise, however, because of the urethane. That this anesthetic may affect the carbohydrate metabolism was suggested by the work of Underhill (10), who showed that adrenalin glycosuria was more readily obtained when urethane was the anesthetic than otherwise. The rise of sugar values which we have found, however, is very striking and difficult to explain. Three possibilities suggest themselves: *a*, It may be the hyperglycemia associated with activity of the sympathetic nervous system; *b*, The reduced total metabolism might be used to explain an accumulation in the blood,—but the respiratory quotients in traumatic shock (11) suggest that at least a normal proportion of carbohydrate is being metabolized; *c*, finally one may look to the liver for an explanation. Several French observers have ascribed shock phenomena to a liver insufficiency, and one might assume that this rise in blood sugar is due to a loss from the glycogen commonly stored there. This might be a direct result of the toxic alterations which may occur in the liver (12).

CONCLUSIONS

1. Animals with marked muscle trauma but without true shock showed only slight changes in total non-protein nitrogen, urea, creatin and sugar in the blood. These constituents, especially the creatin and the sugar, rose markedly as shock developed. In control animals the determined constituents showed no appreciable change.

2. The marked rise in creatin is direct evidence of the presence in the blood of products of muscle necrosis, and is therefore suggestive evidence for the theory of the chemical cause of traumatic shock.

3. The cause of the rise in blood sugar is briefly discussed.

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